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(54) Title: INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

(57) Abstract

The present invention is directed to compounds which inhibit farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. The invention is further directed to chemotherapeutic compositions containing the compounds of this invention and methods for inhibiting farnesyl-protein transferase and the farnesylation of the oncogene protein Ras.

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TITLE OF THE INVENTION

INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

BACKGROUND OF THE INVENTION

- 5 The Ras proteins (Ha-Ras, Ki4a-Ras, Ki4b-Ras and N-Ras) are part of a signalling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Biological and biochemical studies of Ras action indicate that Ras functions like a G-regulatory protein. In the inactive state, Ras is bound to GDP. Upon
10 growth factor receptor activation Ras is induced to exchange GDP for GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and D.M.
15 Willumsen, *Ann. Rev. Biochem.* 62:851-891 (1993)). Mutated *ras* genes (Ha-*ras*, Ki4a-*ras*, Ki4b-*ras* and N-*ras*) are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit a growth
20 stimulatory signal.

Ras must be localized to the plasma membrane for both normal and oncogenic functions. At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus
25 contains a sequence motif termed a "CAAX" or "Cys-Aaa¹-Aaa²-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen *et al.*, *Nature* 310:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-protein transferase or geranylgeranyl-protein
30 transferase, which catalyze the alkylation of the cysteine residue of the CAAX motif with a C₁₅ or C₂₀ isoprenoid, respectively. (S. Clarke., *Ann. Rev. Biochem.* 61:355-386 (1992); W.R. Schafer and J. Rine, *Ann. Rev. Genetics* 30:209-237 (1992)). The Ras protein is one of several proteins that are known to undergo post-translational farnesylation.

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Other farnesylated proteins include the Ras-related GTP-binding proteins such as Rho, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., *J. Biol. Chem.* 269, 14182 (1994) have identified a peroxisome associated protein Pxf which is also 5 farnesylated. James, et al., have also suggested that there are farnesylated proteins of unknown structure and function in addition to those listed above.

Inhibition of farnesyl-protein transferase has been shown to block the growth of Ras-transformed cells in soft agar and to modify 10 other aspects of their transformed phenotype. It has also been demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of the Ras oncprotein intracellularly (N.E. Kohl et al., *Science*, 260:1934-1937 (1993) and G.L. James et al., *Science*, 260:1937-1942 (1993). Recently, it has been shown that an 15 inhibitor of farnesyl-protein transferase blocks the growth of *ras*-dependent tumors in nude mice (N.E. Kohl et al., *Proc. Natl. Acad. Sci U.S.A.*, 91:9141-9145 (1994) and induces regression of mammary and salivary carcinomas in *ras* transgenic mice (N.E. Kohl et al., *Nature Medicine*, 1:792-797 (1995)).

Indirect inhibition of farnesyl-protein transferase *in vivo* 20 has been demonstrated with lovastatin (Merck & Co., Rahway, NJ) and compactin (Hancock et al., *ibid*; Casey et al., *ibid*; Schafer et al., *Science* 245:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate limiting enzyme for the production of polyisoprenoids including 25 farnesyl pyrophosphate. Farnesyl-protein transferase utilizes farnesyl pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX box with a farnesyl group (Reiss et al., *Cell*, 62:81-88 (1990); Schaber et al., *J. Biol. Chem.*, 265:14701-14704 (1990); Schafer et al., *Science*, 249:1133-1139 (1990); Manne et al., *Proc. Natl. Acad. Sci USA*, 87:7541-7545 (1990)). Inhibition of farnesyl pyrophosphate 30 biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane localization in cultured cells. However, direct inhibition of farnesyl-protein transferase would be more specific and attended by fewer side

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effects than would occur with the required dose of a general inhibitor of isoprene biosynthesis.

- Inhibitors of farnesyl-protein transferase (FPTase) have been described in two general classes. The first are analogs of farnesyl diphosphate (FPP), while the second class of inhibitors is related to the protein substrates (e.g., Ras) for the enzyme. The peptide derived inhibitors that have been described are generally cysteine containing molecules that are related to the CAAX motif that is the signal for protein prenylation. (Schaber *et al.*, *ibid*; Reiss *et. al.*, *ibid*; Reiss *et al.*, 5 *PNAS*, 88:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as alternate substrates for the farnesyl-protein transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl *et al.*, *Science*, 10 260:1934-1937 (1993); Graham, et al., *J. Med. Chem.*, 37, 725 (1994)).
- 15 In general, deletion of the thiol from a CAAX derivative has been shown to dramatically reduce the inhibitory potency of the compound. However, the thiol group potentially places limitations on the therapeutic application of FPTase inhibitors with respect to pharmacokinetics, pharmacodynamics and toxicity. Therefore, a 20 functional replacement for the thiol is desirable.

It has recently been reported that farnesyl-protein transferase inhibitors are inhibitors of proliferation of vascular smooth muscle cells and are therefore useful in the prevention and therapy of arteriosclerosis and diabetic disturbance of blood vessels (JP H7-25 112930).

It has recently been disclosed that certain tricyclic compounds which optionally incorporate a piperidine moiety are 30 inhibitors of FPTase (WO 95/10514, WO 95/10515 and WO 95/10516). Imidazole-containing inhibitors of farnesyl protein transferase have also been disclosed (WO 95/09001 and EP 0 675 112 A1).

It is, therefore, an object of this invention to develop peptidomimetic compounds that do not have a thiol moiety, and that will inhibit farnesyl-protein transferase and thus, the post-translational farnesylation of proteins. It is a further object of this invention to

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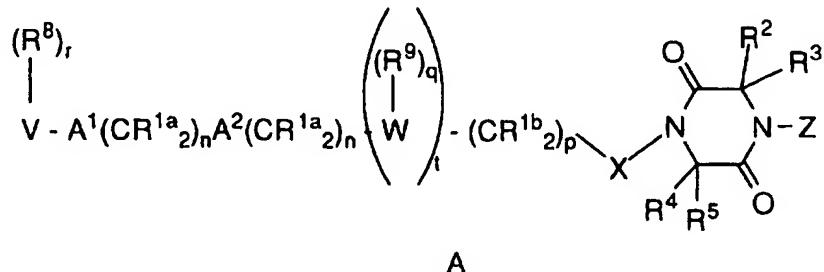
develop chemotherapeutic compositions containing the compounds of this invention and methods for producing the compounds of this invention.

5 SUMMARY OF THE INVENTION

The present invention comprises peptidomimetic 2,5-diketopiperazine-containing compounds which inhibit the farnesyl-protein transferase. The instant compounds lack a thiol moiety and thus offer unique advantages in terms of improved pharmacokinetic behavior
 10 in animals, prevention of thiol-dependent chemical reactions, such as rapid autoxidation and disulfide formation with endogenous thiols, and reduced systemic toxicity. Further contained in this invention are chemotherapeutic compositions containing these farnesyl transferase inhibitors and methods for their production.

15

The compounds of this invention are illustrated by the formula A:

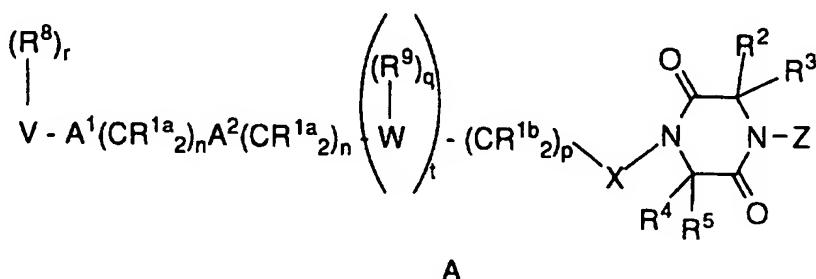


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DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. In a first embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula A:

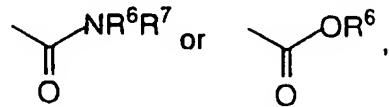


wherein:

- 10 R^{1a} and R^{1b} are independently selected from:
 - a) hydrogen,
 - b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
 - c) unsubstituted or substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, and R¹¹OC(O)NR¹⁰-;
- 15 R^2 and R^4 are independently selected from: H; unsubstituted or substituted C₁-8 alkyl, unsubstituted or substituted C₂-8 alkenyl,
- 20
- 25

- 6 -

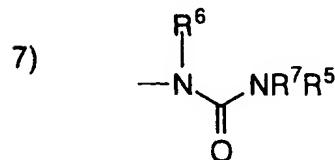
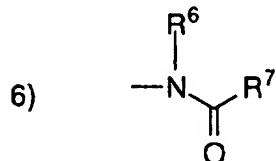
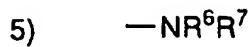
unsubstituted or substituted C₂-8 alkynyl, unsubstituted or substituted aryl,



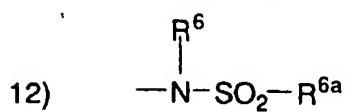
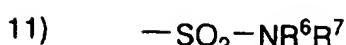
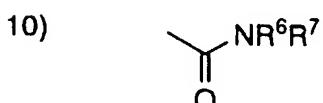
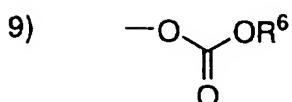
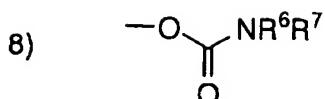
unsubstituted or substituted heterocycle,

wherein the substituted group is substituted with one or more of:

- 1) aryl or heterocycle, unsubstituted or substituted with:
 - 5 a) C₁-4 alkyl,
 - b) (CH₂)_pOR⁶,
 - c) (CH₂)_pNR⁶R⁷,
 - d) halogen,
 - e) CN,
 - f) aryl or heteroaryl,
 - 10 g) perfluoro-C₁-4 alkyl, or
 - h) SR^{6a}, S(O)R^{6a}, SO₂R^{6a},
- 2) C₃-6 cycloalkyl,
- 3) OR⁶,
- 15 4) SR^{6a}, S(O)R^{6a}, or SO₂R^{6a},



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15) N_3 ,

16) F, or

17) perfluoro-C₁₋₄-alkyl;

5 R³ and R⁵ are selected from H and CH₃; or

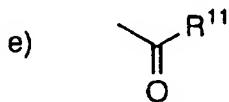
R² and R³ or R⁴ and R⁵ attached to the same C atom are combined to form -(CH₂)_u- wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR¹⁰)-;

10

R⁶, R⁷ and R^{7a} are independently selected from: H; C₁₋₄ alkyl, C₃₋₆ cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

- 8 -

- a) C₁-4 alkoxy,
 - b) aryl or heterocycle,
 - c) halogen,
 - d) HO,

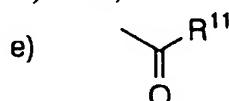


R^6 and R^7 may be joined in a ring;
 R^7 and R^{7a} may be joined in a ring;

10

R^{6a} is selected from: C₁-4 alkyl, C₃-6 cycloalkyl, heterocycle, aryl, unsubstituted or substituted with:

- a) C1-4 alkoxy,
 - b) aryl or heterocycle,
 - c) halogen,
 - d) HO.



- f) $-\text{SO}_2\text{R}^{11}$, or
 g) $\text{N}(\text{R}^{10})_2$;

20 R8 is independently selected from:

- a) hydrogen,
 - b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
 - c) C₁-C₆ alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,

- 9 -

$R^{11}S(O)m-$, $R^{10}C(O)NH-$, $(R^{10})_2NC(O)-$, $R^{10}_2N-C(NR^{10})-$, CN, $R^{10}C(O)-$, N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;

5 R⁹ is selected from:

- a) hydrogen,
- b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

15

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

20

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

25 V is selected from:

- a) hydrogen,
- b) heterocycle,
- c) aryl,
- d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- e) C₂-C₂₀ alkenyl,

provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

- 10 -

W is a heterocycle;

X is a bond, -CH₂-, -C(=O)-, or -S(=O)_m-;

5

Z is selected from:

- 10 1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroaryl methyl, arylsulfonyl, heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:

15 a) C₁-4 alkyl, unsubstituted or substituted with:
 C₁-4 alkoxy, NR⁶R⁷, C₃-6 cycloalkyl, aryl, heterocycle, HO, -S(O)_mR^{6a}, or -C(O)NR⁶R⁷,

15 b) aryl or heterocycle,

15 c) halogen,

15 d) OR⁶,

15 e) NR⁶R⁷,

15 f) CN,

15 g) NO₂,

20 h) CF₃;

20 i) -S(O)_mR^{6a},

20 j) -C(O)NR⁶R⁷, or

20 k) C₃-C₆ cycloalkyl; or

- 25 2) unsubstituted C₁-C₆ alkyl, substituted C₁-C₆ alkyl, unsubstituted C₃-C₆ cycloalkyl or substituted C₃-C₆ cycloalkyl, wherein the substituted C₁-C₆ alkyl and substituted C₃-C₆ cycloalkyl is substituted with one or two of the following:

30 a) C₁-4 alkoxy,

30 b) NR⁶R⁷,

30 c) C₃-6 cycloalkyl,

30 d) -NR⁶C(O)R⁷,

30 e) HO,

30 f) -S(O)_mR^{6a},

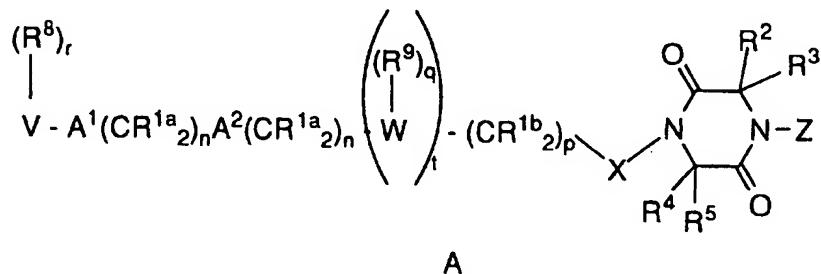
- 11 -

- g) halogen, or
- h) perfluoroalkyl;

- | | | |
|----|------|--|
| | m is | 0, 1 or 2; |
| 5 | n is | 0, 1, 2, 3 or 4; |
| | p is | 0, 1, 2, 3 or 4; |
| | q is | 1 or 2; |
| | r is | 0 to 5, provided that r is 0 when V is hydrogen; |
| | t is | 0 or 1; and |
| 10 | u is | 4 or 5; |

or the pharmaceutically acceptable salts thereof.

- 15 A preferred embodiment of the compounds of this invention is illustrated by the following formula:



wherein:

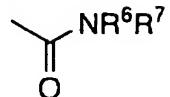
- 20 R^{1a} is independently selected from: hydrogen or C₁-C₆ alkyl;

- R^{1b} is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, R¹⁰O-, -N(R¹⁰)₂ or C₂-C₆ alkenyl,
- 25 c) unsubstituted or substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O- and -N(R¹⁰)₂;

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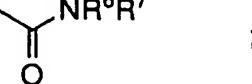
R³ and R⁵ are independently selected from H and CH₃;



R² and R⁴ are independently selected from H; alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

- 1) aryl,
- 2) heterocycle,
- 3) OR⁶,
- 4) SR^{6a}, SO₂R^{6a}, or
- 5)

10



R⁶, R⁷ and R^{7a} are independently selected from:

H; C₁-4 alkyl, C₃-6 cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

- a) C₁-4 alkoxy,
- b) halogen, or
- c) aryl or heterocycle;

R^{6a} is selected from:

- 20 C₁-4 alkyl or C₃-6 cycloalkyl,
unsubstituted or substituted with:
 - a) C₁-4 alkoxy,
 - b) halogen, or
 - c) aryl or heterocycle;

25

R⁸ is independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, CN, NO₂,
- 30 (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or
R¹¹OC(O)NR¹⁰-, and

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- c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,

5 R⁹ is selected from:

- a) hydrogen,
b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or
10 R¹¹OC(O)NR¹⁰-, and
c) C₁-C₆ alkyl unsubstituted or substituted by C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or
15 R¹¹OC(O)NR¹⁰-,

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

20 R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, O, -N(R¹⁰)-, or S(O)_m;

V is selected from:

- 25 a) hydrogen,
b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thieryl,
c) aryl,
30 d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
e) C₂-C₂₀ alkenyl, and

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provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

5 W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or isoquinolinyl;

X is -CH₂- or -C(=O)-;

10 Z is selected from:

1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:

15 a) C₁-4 alkyl, unsubstituted or substituted with: C₁-4 alkoxy, NR⁶R⁷, C₃-6 cycloalkyl, aryl, heterocycle, HO, -S(O)_mR^{6a}, or -C(O)NR⁶R⁷,

b) aryl or heterocycle,

c) halogen,

d) OR⁶,

e) NR⁶R⁷,

f) CN,

g) NO₂,

h) CF₃;

25 i) -S(O)_mR^{6a},

j) -C(O)NR⁶R⁷, or

k) C₃-C₆ cycloalkyl; or

2) unsubstituted C₁-C₆ alkyl, substituted C₁-C₆ alkyl, unsubstituted C₃-C₆ cycloalkyl or substituted C₃-C₆

30 cycloalkyl, wherein the substituted C₁-C₆ alkyl and substituted C₃-C₆ cycloalkyl is substituted with one or two of the following:

a) C₁-4 alkoxy,

b) NR⁶R⁷,

- 15 -

c) C₃-6 cycloalkyl,

d) -NR⁶C(O)R⁷,

e) HO,

f) -S(O)_mR^{6a},

5 g) halogen, or

h) perfluoroalkyl;

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

10 p is 0, 1, 2, 3 or 4;

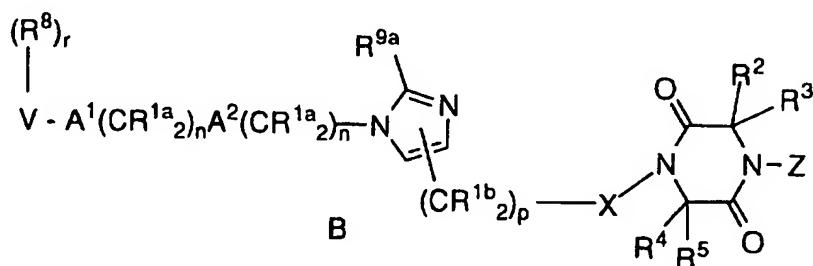
r is 0 to 5, provided that r is 0 when V is hydrogen;

t is 0 or 1; and

u is 4 or 5;

15 or the pharmaceutically acceptable salts thereof.

A preferred embodiment of the compounds of this invention are illustrated by the formula B:



20 wherein:

R^{1a} is selected from: hydrogen or C₁-C₆ alkyl;

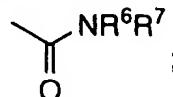
R^{1b} is independently selected from:

- 25 a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, R¹⁰O-, -N(R¹⁰)₂ or C₂-C₆ alkenyl,

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- c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, or -N(R¹⁰)₂;

R³ and R⁵ are independently selected from H and CH₃;



- 5 R² and R⁴ are independently selected from H; or C₁-5 alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

- 1) aryl,
- 2) heterocycle,
- 3) OR⁶,
- 4) SR^{6a}, SO₂R^{6a}, or
- 5)

10

R⁶ and R⁷ are independently selected from:

- 15 a) hydrogen,
- b) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 20 c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,

R⁸ is independently selected from:

- 25 a) hydrogen,
- b) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and

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c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

5 R^{9a} is hydrogen or methyl;

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

10 R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, O, -N(R¹⁰)-, or S(O)_m;

15 V is selected from:

a) hydrogen,
b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,

20 c) aryl,

d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and

e) C₂-C₂₀ alkenyl, and

25 provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

X is -CH₂-;

30 Z is selected from:

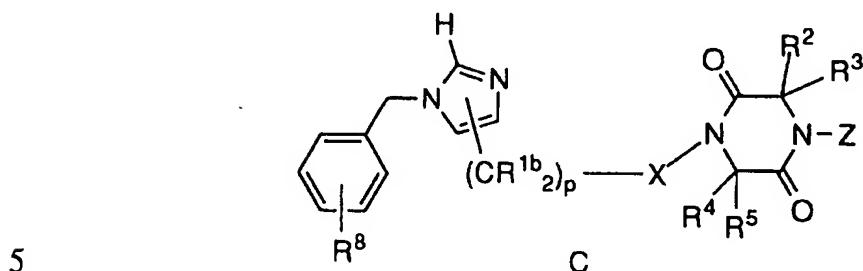
1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroaryl methyl, arylsulfonyl, heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:

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- a) C₁-4 alkyl, unsubstituted or substituted with:
C₁-4 alkoxy, NR⁶R⁷, C₃-6 cycloalkyl, aryl,
heterocycle, HO, -S(O)_mR^{6a}, or -C(O)NR⁶R⁷,
 - b) aryl or heterocycle,
 - c) halogen,
 - d) OR⁶,
 - e) NR⁶R⁷,
 - f) CN,
 - g) NO₂,
 - h) CF₃;
 - i) -S(O)_mR^{6a},
 - j) -C(O)NR⁶R⁷, or
 - k) C₃-C₆ cycloalkyl; or
- 2) unsubstituted C₁-C₆ alkyl, substituted C₁-C₆ alkyl,
unsubstituted C₃-C₆ cycloalkyl or substituted C₃-C₆
cycloalkyl, wherein the substituted C₁-C₆ alkyl and substituted
C₃-C₆ cycloalkyl is substituted with one or two of the
following:
- a) C₁-4 alkoxy,
 - b) NR⁶R⁷,
 - c) C₃-6 cycloalkyl,
 - d) -NR⁶C(O)R⁷,
 - e) HO,
 - f) -S(O)_mR^{6a},
 - g) halogen, or
 - h) perfluoroalkyl;
- m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
30 p is 0, 1, 2, 3 or 4; and
r is 0 to 5, provided that r is 0 when V is hydrogen;
or the pharmaceutically acceptable salts thereof.

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In a more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula C:

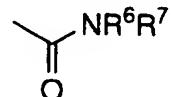


wherein:

R^{1b} is independently selected from:

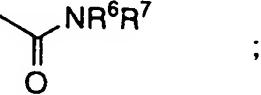
- 10 a) hydrogen,
 b) aryl, heterocycle, cycloalkyl, $R^{10}O-$, $-N(R^{10})_2$ or C₂-C₆
 alkenyl,
 c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
 heterocycle, cycloalkyl, alkenyl, $R^{10}O-$, or $-N(R^{10})_2$;

15 R³ and R⁵ are independently selected from H and CH₃;



R^2 and R^4 are independently selected from H; O or C₁₋₅ alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

- 20 1) aryl,
 2) heterocycle,
 3) OR⁶,
 4) SR^{6a}, SO₂R^{6a}, or
 5) -NR^{6B}⁷



25 R⁶ and R⁷ are independently selected from:

- 20 -

- a) hydrogen,
 - b) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
 - c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- 10 R⁸ is independently selected from:
- a) hydrogen,
 - b) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
 - c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- 15 R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;
- 20 R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

25 X is -CH₂-;

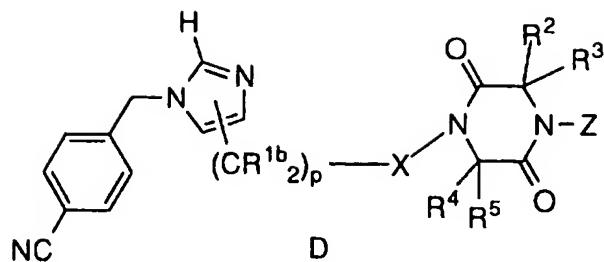
Z is selected from:

- 30 1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:
- a) C₁-4 alkyl, unsubstituted or substituted with: C₁-4 alkoxy, NR⁶R⁷, C₃-6 cycloalkyl, aryl, heterocycle, HO, -S(O)_mR^{6a}, or -C(O)NR⁶R⁷,

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- b) aryl or heterocycle,
 - c) halogen,
 - d) OR⁶,
 - e) NR⁶R⁷,
 - 5 f) CN,
 - g) NO₂,
 - h) CF₃;
 - i) -S(O)_mR^{6a},
 - j) -C(O)NR⁶R⁷, or
 - 10 k) C₃-C₆ cycloalkyl; or
- 2) unsubstituted C₁-C₆ alkyl, substituted C₁-C₆ alkyl, unsubstituted C₃-C₆ cycloalkyl or substituted C₃-C₆ cycloalkyl, wherein the substituted C₁-C₆ alkyl and substituted C₃-C₆ cycloalkyl is substituted with one or two of the following:
- a) C₁-4 alkoxy,
 - b) NR⁶R⁷,
 - c) C₃-6 cycloalkyl,
 - d) -NR⁶C(O)R⁷,
 - 15 e) HO,
 - f) -S(O)_mR^{6a},
 - g) halogen, or
 - h) perfluoroalkyl;
- 20 25 m is 0, 1 or 2; and
p is 0, 1, 2, 3 or 4;
- or the pharmaceutically acceptable salts thereof.
- 30 In a second more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula D:

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wherein:

R^{1b} is independently selected from:

- 5 a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, $R^{10}O-$, $-N(R^{10})_2$ or C₂-C₆ alkenyl,
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O-$, or $-N(R^{10})_2$;

10 R^2 and R^4 are independently selected from: hydrogen or C₁-C₆ alkyl;

R^3 and R^5 are hydrogen;

15 R^6 and R^7 are independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, $R^{10}O-$, $R^{10}C(O)NR^{10}-$, CN, NO₂, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$, and
- c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, $R^{10}O-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$;

25 R^{10} is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

R^{11} is independently selected from C₁-C₆ alkyl and aryl;

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X is -CH₂-;

Z is mono- or bicyclic aryl, mono- or bicyclic heteroaryl,
mono- or bicyclic arylmethyl, mono- or bicyclic
heteroarylmethyl, mono- or bicyclic arylsulfonyl,
mono- or bicyclic heteroarylsulfonyl, unsubstituted or
substituted with one or two of the following:
5 1) C₁-4 alkyl, unsubstituted or substituted with:
 a) C₁-4 alkoxy,
10 b) NR⁶R⁷,
 c) C₃-6 cycloalkyl,
 d) aryl or heterocycle,
 e) HO,
 f) -S(O)_mR⁶, or
15 g) -C(O)NR⁶R⁷,
 2) aryl or heterocycle,
 3) halogen,
 4) OR⁶,
 5) NR⁶R⁷,
20 6) CN,
 7) NO₂,
 8) CF₃;
 9) -S(O)_mR⁶,
 10) -C(O)NR⁶R⁷, or
25 11) C₃-C₆ cycloalkyl;

m is 0, 1 or 2; and

p is 0, 1, 2, 3 or 4;

30 or the pharmaceutically acceptable salts thereof.

The preferred compounds of this invention are as follows:

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4-[1-(4-Cyanobenzyl)-5-imidazolylmethyl]-1-(3-chlorophenyl)-piperazine-2,5-dione

5 (S)-3-n-Butyl-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-(3-chlorophenyl)piperazine-2,5-dione

1-(3-Chlorophenyl)-4-[(3-(4-cyanobenzyl)pyridin-4-yl)methyl]piperazin-2,5-dione

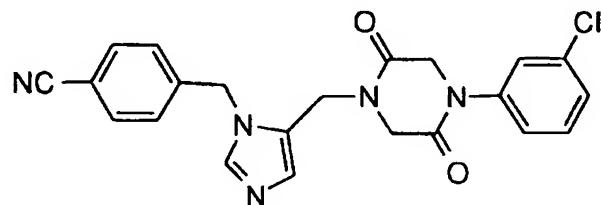
10 4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-phenylpiperazine-2,5-dione and

4-benzyl-1-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-piperazine-2,5-dione

15 or the pharmaceutically acceptable salts thereof.

Specific examples of the compounds of the invention are:

20 4-[1-(4-Cyanobenzyl)-5-imidazolylmethyl]-1-(3-chlorophenyl)-piperazine-2,5-dione



25

or the pharmaceutically acceptable salts thereof.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical

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isomers, being included in the present invention. When any variable (e.g. aryl, heterocycle, R¹, R² etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents/or variables are
5 permissible only if such combinations result in stable compounds.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen
10 bridge. "Halogen" or "halo" as used herein means fluoro, chloro, bromo and iodo.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements
15 include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl.

The term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or
20 unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the
25 creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl,
30 dihydrobenzothiopyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl,

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pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, 5 thienofuryl, thienothienyl, and thietyl.

As used herein, "heteroaryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four carbon atoms are replaced by heteroatoms selected from the group 10 consisting of N, O, and S. Examples of such heterocyclic elements include, but are not limited to, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, 15 dihydrobenzothiopyranyl sulfone, furyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiazolyl, thienofuryl, 20 thienothienyl, and thietyl.

As used herein in the definition of R² and R³, the term "the substituted group" intended to mean a substituted C₁₋₈ alkyl, substituted C₂₋₈ alkenyl, substituted C₂₋₈ alkynyl, substituted aryl or substituted heterocycle from which the substituent(s) R² and R³ are selected.

As used herein in the definition of R⁶, R^{6a}, R⁷ and R^{7a}, 25 the substituted C₁₋₈ alkyl, substituted C₃₋₆ cycloalkyl, substituted aroyl, substituted aryl, substituted heteroaroyl, substituted arylsulfonyl, substituted heteroarylsulfonyl and substituted heterocycle include moieties containing from 1 to 3 substituents in addition to the point of 30 attachment to the rest of the compound.

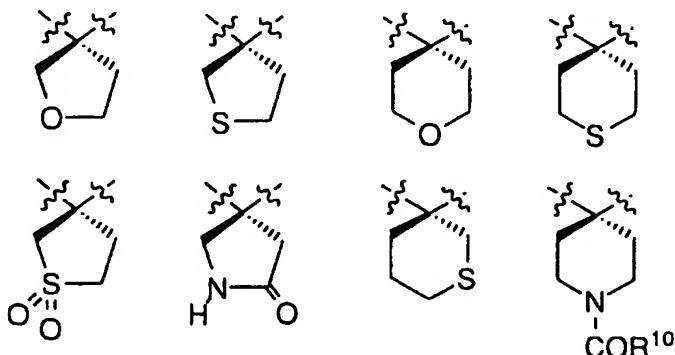
When R² and R³ are combined to form -(CH₂)_u-, cyclic moieties are formed. Examples of such cyclic moieties include, but are not limited to:

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In addition, such cyclic moieties may optionally include a heteroatom(s). Examples of such heteroatom-containing cyclic moieties include, but are not limited to:

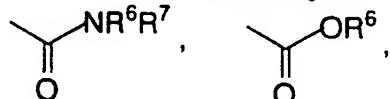
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Lines drawn into the ring systems from substituents (such as from R², R³, R⁴ etc.) indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

10 Preferably, R^{1a} and R^{1b} are independently selected from: hydrogen, -N(R¹⁰)₂, R¹⁰C(O)NR¹⁰- or unsubstituted or substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted phenyl, -N(R¹⁰)₂, R¹⁰O- and R¹⁰C(O)NR¹⁰-.

15 Preferably, R² is selected from: H,



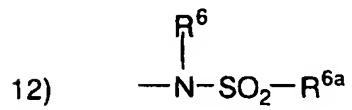
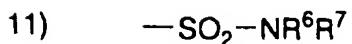
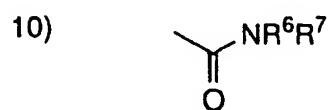
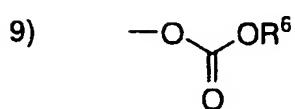
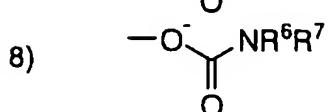
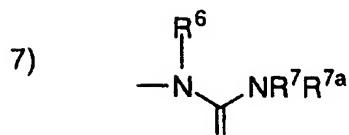
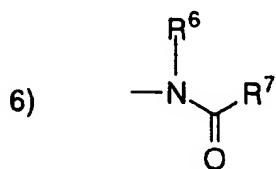
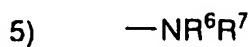
and an unsubstituted or substituted group, the group selected from C₁-8 alkyl, C₂-8 alkenyl and C₂-8 alkynyl;

wherein the substituted group is substituted with one or more of:

- 20 1) aryl or heterocycle, unsubstituted or substituted with:
a) C₁-4 alkyl,
b) (CH₂)_pOR⁶,

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- 5 c) $(CH_2)_pNR^6R^7$,
 d) halogen,
 2) C₃-6 cycloalkyl,
 3) OR⁶,
 4) SR^{6a}, S(O)R^{6a}, SO₂R^{6a},



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15) N₃, or

16) F.

Preferably, R³ is selected from: hydrogen and C₁-C₆ alkyl.

Preferably, R⁴ and R⁵ are hydrogen.

5 Preferably, R⁶, R⁷ and R^{7a} is selected from: hydrogen, unsubstituted or substituted C₁-C₆ alkyl, unsubstituted or substituted aryl and unsubstituted or substituted cycloalkyl.

10 Preferably, R^{6a} is unsubstituted or substituted C₁-C₆ alkyl, unsubstituted or substituted aryl and unsubstituted or substituted cycloalkyl.

Preferably, R⁹ is hydrogen or methyl. Most preferably, R⁹ is hydrogen.

Preferably, R¹⁰ is selected from H, C₁-C₆ alkyl and benzyl.

15 Preferably, A¹ and A² are independently selected from: a bond, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)- and -N(R¹⁰)S(O)₂-.

Preferably, V is selected from hydrogen, heterocycle and aryl. More preferably, V is phenyl.

20 Preferably, Z is selected from unsubstituted or substituted phenyl, unsubstituted or substituted naphthyl, unsubstituted or substituted pyridyl, unsubstituted or substituted furanyl, unsubstituted or substituted thienyl and unsubstituted or substituted alkyl. More preferably, Z is unsubstituted or substituted phenyl.

- 25 - Preferably, W is selected from imidazolyl, imidazolyl, oxazolyl, pyrazolyl, pypyridinyl, thiazolyl and pyridyl. More preferably, W is selected from imidazolyl and pyridyl.

- 30 -

Preferably, n and r are independently 0, 1, or 2.

Preferably p is 1, 2 or 3.

Preferably s is 0.

Preferably t is 1.

5 Preferably X is -CH₂-.

- It is intended that the definition of any substituent or variable (e.g., R^{1a}, R⁹, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, -N(R¹⁰)₂ represents -NHH, -NHCH₃, -NHC₂H₅, etc. It is understood
10 that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

- 15 The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic,
20 sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic,
25 isethionic, trifluoroacetic and the like.

- The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods.
Generally, the salts are prepared either by ion exchange
30 chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the Schemes 1-14, in

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addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures.

- These reactions may be employed in a linear sequence to
- 5 provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes.

Synopsis of Schemes 1-14:

- 10 The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. 2,5-Diketopiperazines can be generally prepared as shown in Scheme 1. Amination of the suitably substituted bromoacetate I provides the N-substituted ester II. This is then reacted with a protected
- 15 substituted acetyl chloride to provide the secondary amide III; subsequent to acid deprotection, ring closure to the diketopiperazine VI occurs concurrently with reductive alkylation with an aldehyde such as the protected imidazolyl aldehyde V. The imidazolyl protecting group may be removed under acidic conditions such as trifluoroacetic acid in
- 20 methylene chloride. Alternatively, the imidazolyl may be alkylated and then deprotected to provide compounds such as VIII

- The intermediate IV can be cyclized and reductively alkylated with a variety of aldehydes, such as IX. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, 1988, 67, 69-75), from the appropriate amino acid (Scheme 2). The reductive alkylation can be accomplished at pH 5-7 with a variety of reducing agents, such as sodium triacetoxyborohydride or sodium cyanoborohydride in a solvent such as dichloroethane, methanol or
- 25 dimethylformamide. The product X can be deprotected to give the final compounds XI with trifluoroacetic acid in methylene chloride. The final product XI is isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine XI can further be selectively protected to obtain XII,

which can subsequently be reductively alkylated with a second aldehyde to obtain **XIII**. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole **XV** can be accomplished by literature procedures.

5 As shown in Scheme 3, the imidazole acetic acid **XVI** can be converted to the acetate **XVII** by standard procedures, and **XVII** can be first reacted with an alkyl halide, then treated with refluxing methanol to provide the regiospecifically alkylated imidazole acetic acid ester **XIX**. The ester is hydrolyzed and the acid converted to the acid
10 chloride. Reaction with the suitably substituted lithium diketopiperazine **XXI** in the presence of condensing reagents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) leads to acylated products such as **XXII**.

15 Scheme 3a illustrates an alternative preparation of the instant compounds which incorporate the preferred benzylimidazolyl moiety. As shown in the scheme, cyclization affords the key intermediate 1-(1-benzylimidazol-5-yl)piperazine-2,5-dione, which can then be reacted with a suitably substituted triaryl bismuth reagent or other suitable electrophiles (Scheme 3b).

20 If the intermediate **IV** is cyclized/reductively alkylated with an aldehyde which also has a protected hydroxyl group, such as **XXIII** in Scheme 4, the protecting groups can be subsequently removed to unmask the hydroxyl group (Schemes 4, 5). The alcohol can be oxidized under standard conditions to *e.g.* an aldehyde, which can then
25 be reacted with a variety of organometallic reagents such as Grignard reagents, to obtain secondary alcohols such as **XXVII**. In addition, the fully deprotected amino alcohol **XXV** can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as **XXIX** (Scheme 5), or tertiary amines.

30 The Boc protected amino alcohol **XXV** can also be utilized to synthesize 4-(2-aziridinylmethyl)-2,5-diketopiperazines such as **XXX** (Scheme 6). Treating **XXV** with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide led to the formation of aziridine **XXX**. The aziridine reacted in the presence of a nucleophile,

such as a thiol, in the presence of base to yield, after deprotection, the ring-opened product XXXII.

In addition, the intermediate IV can be reacted with aldehydes derived from amino acids such as O-alkylated tyrosines, 5 according to standard procedures, to obtain compounds such as XXXV as shown in Scheme 7. When R' is an aryl group, XXXV can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce XXXVI. Alternatively, the amine protecting group in XXXV can be removed, and O-alkylated phenolic amines such 10 as XXXVII produced.

Reaction Scheme 8 provides an illustrative example the synthesis of compounds of the instant invention wherein the substituents R⁴ and R⁵ are combined to form - (CH₂)_u -. For example, 1-aminocyclohexane-1-carboxylic acid XXXVIII can be converted to the 15 spirodiketopiperazine an intermediate IXL essentially according to the procedures outlined in Schemes 1 and 2. The intermediate IXL can be deprotected as before, and carried on to final products as described in Schemes 3-8. It is understood that reagents utilized to provide the imidazolylalkyl substituent may be readily replaced by other reagents 20 well known in the art and readily available to provide other N-substituents on the diketopiperazine.

Scheme 9 illustrates the use of an optionally substituted homoserine lactone XLII to prepare a Boc-protected intermediate XLIII. Intermediate XLIII may be deprotected and cyclized/reductively 25 alkylated or acylated as illustrated in the previous Schemes. Alternatively, the hydroxyl moiety of diketopiperazine XLIV may be mesylated and displaced by a suitable nucleophile, such as the sodium salt of ethane thiol, to provide an the sulfide XLV. Diketopiperazine XLIV may also be oxidized to provide the carboxylic acid on 30 diketopiperazine XLVI, which can be further utilized to form an ester or amide moiety.

Amino acids of the general formula XLVIII which have a sidechain not found in natural amino acids may be prepared by the

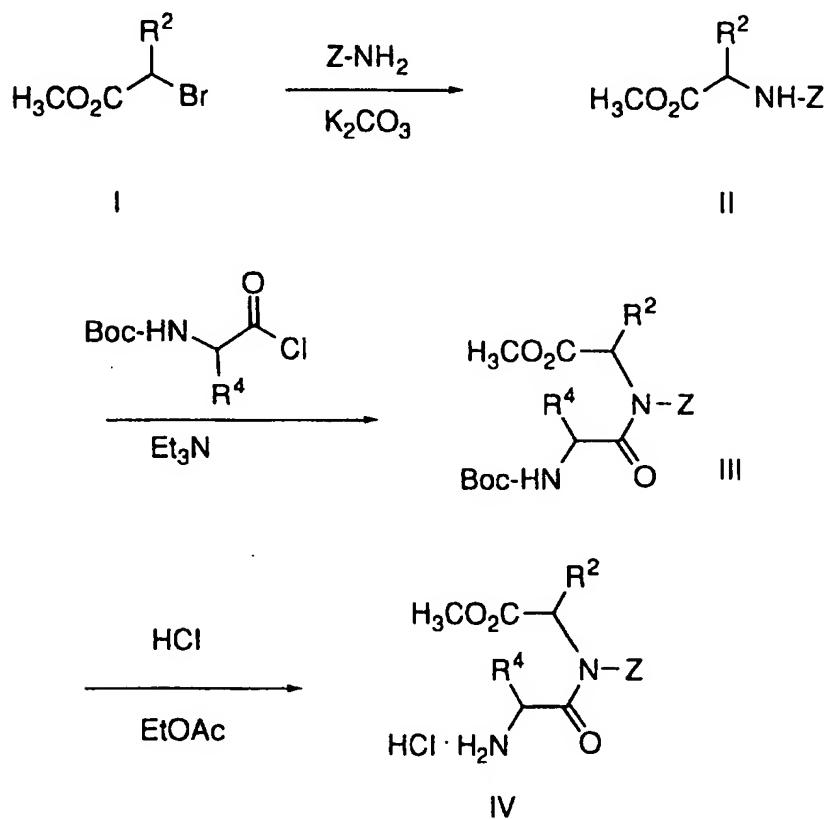
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reactions illustrated in Scheme 10 starting with the readily prepared imine XLIX.

Schemes 11-14 illustrate syntheses of suitably substituted aldehydes useful in the syntheses of the instant compounds wherein the variable W is present as a pyridyl moiety. Similar synthetic strategies for preparing alkanols that incorporate other heterocyclic moieties for variable W are also well known in the art.

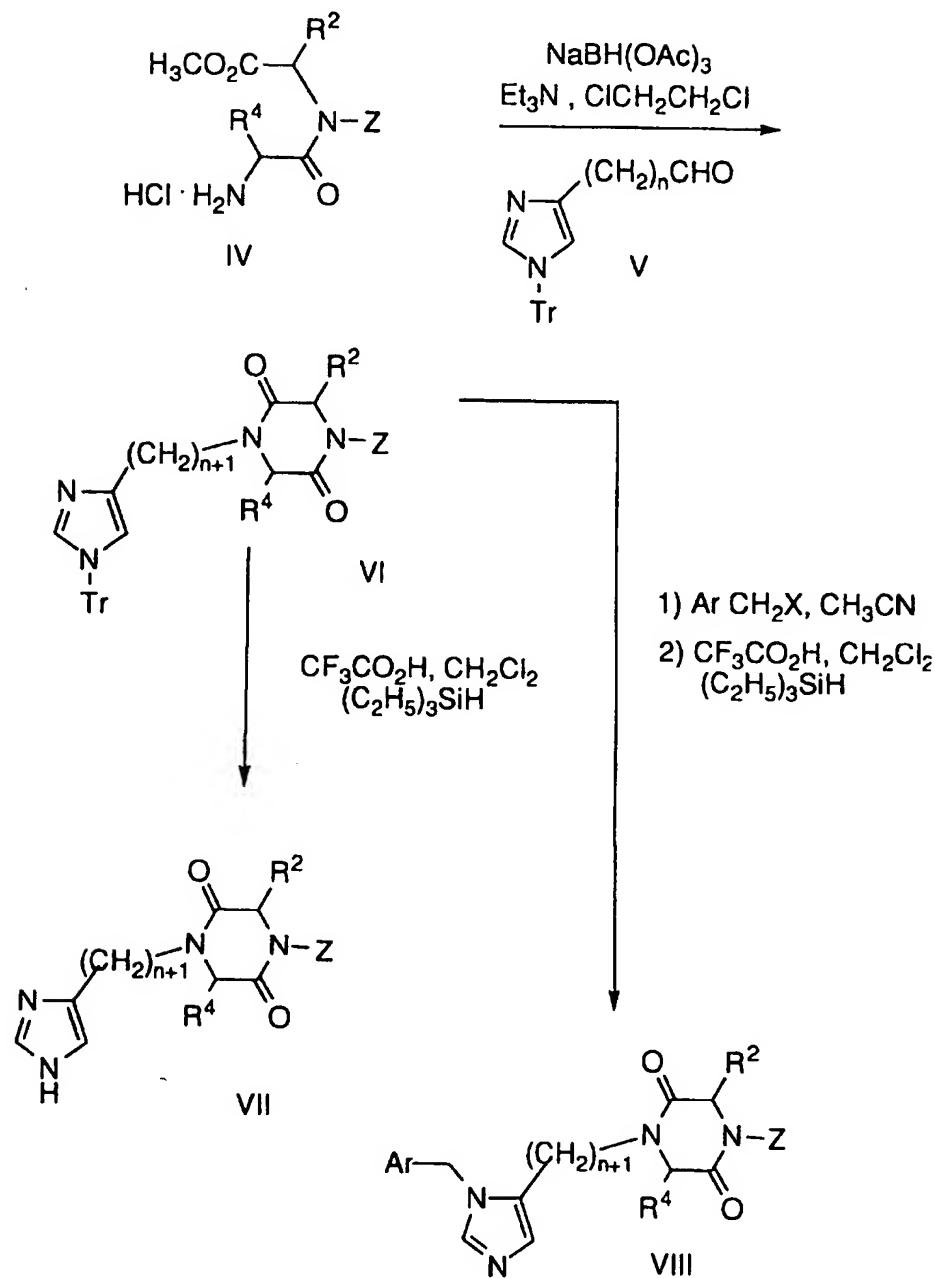
SCHEME 1

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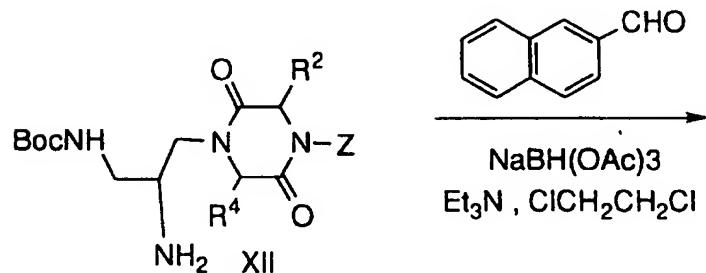
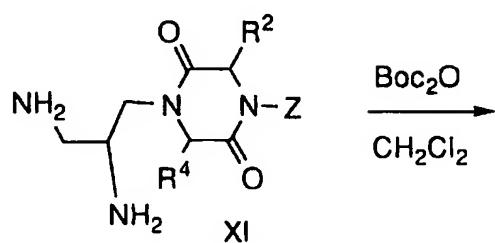
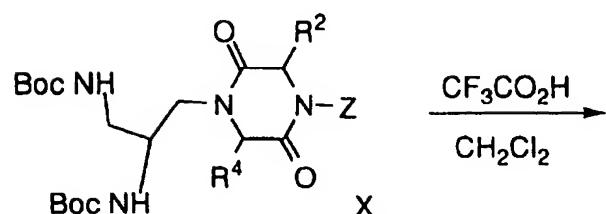
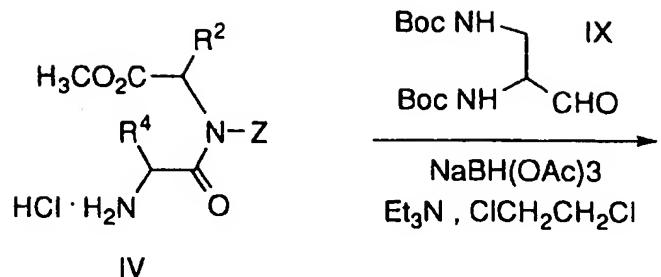
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SCHEME 1 (continued)



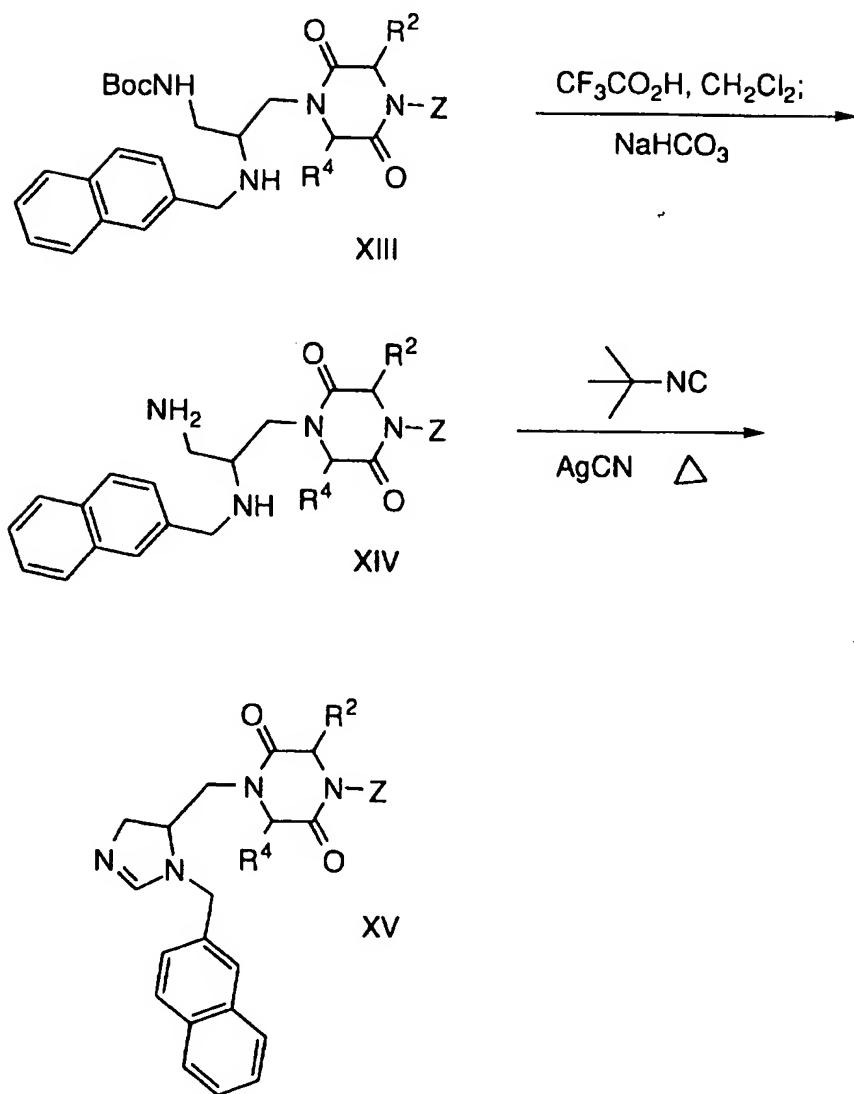
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SCHEME 2



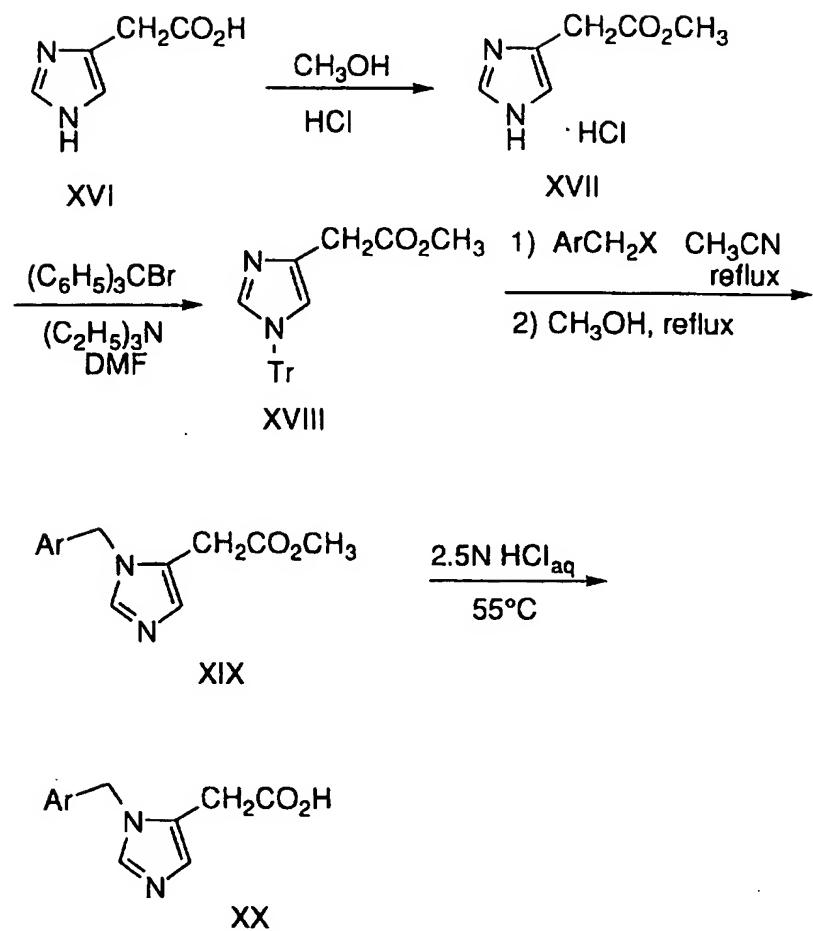
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SCHEME 2 (continued)



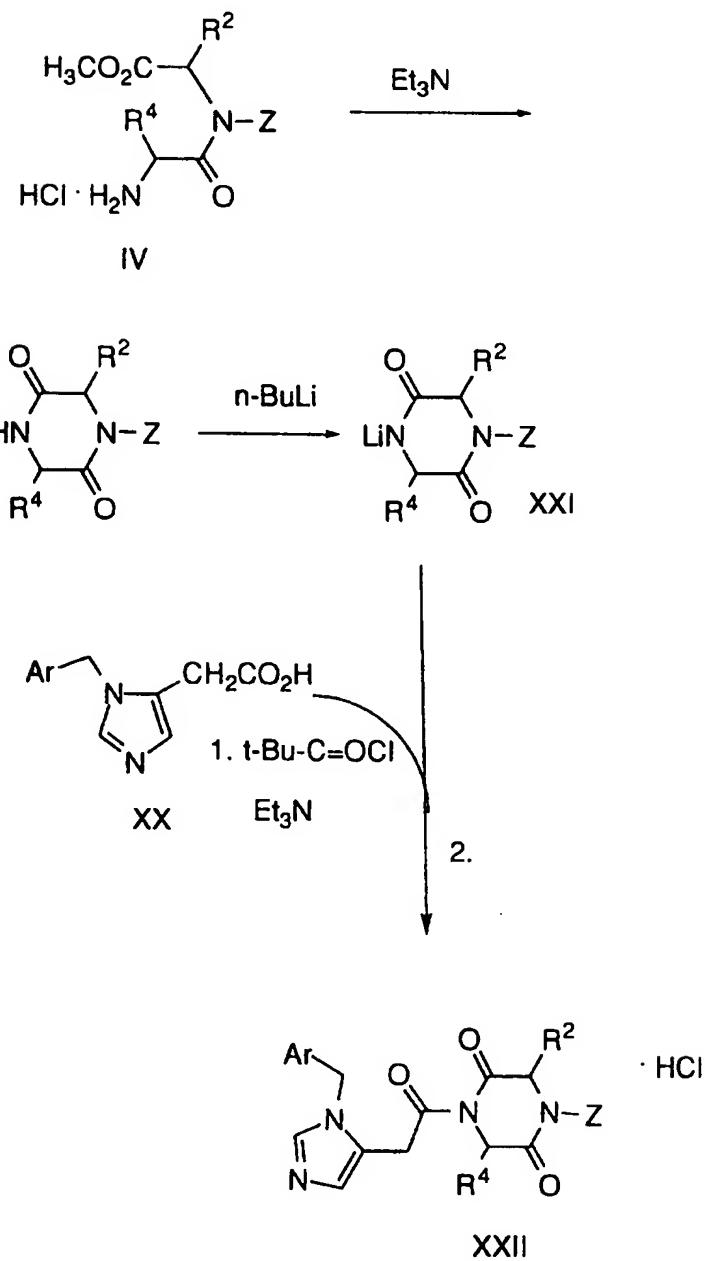
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SCHEME 3



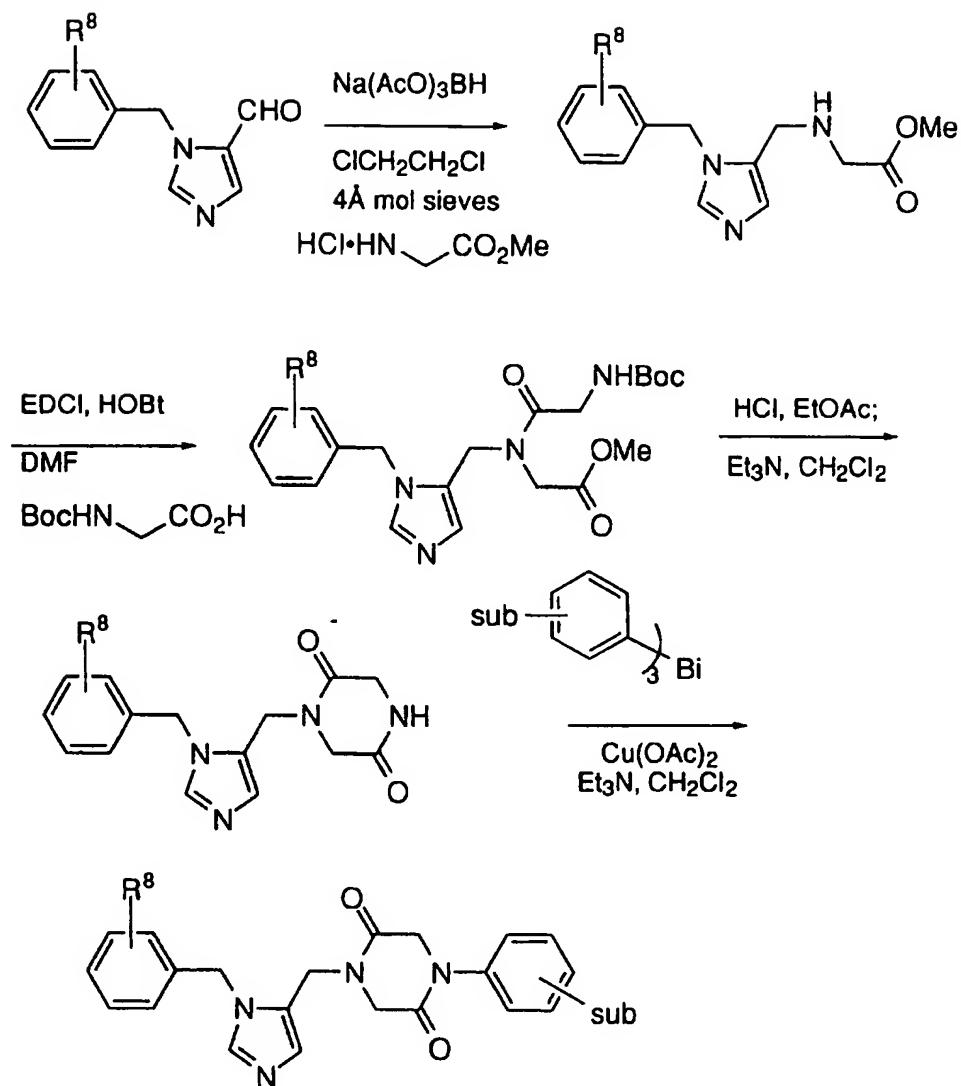
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SCHEME 3 (continued)



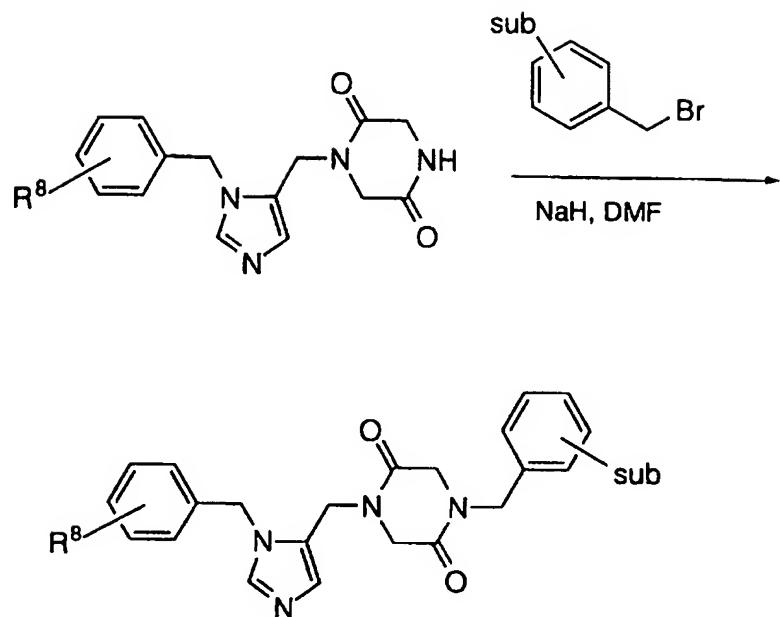
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SCHEME 3a



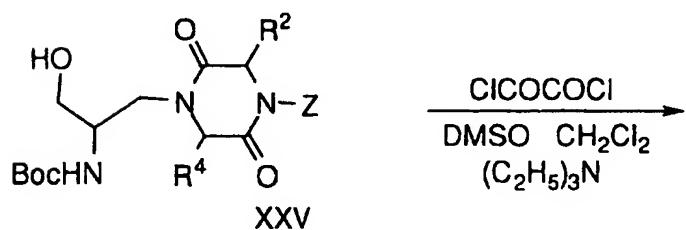
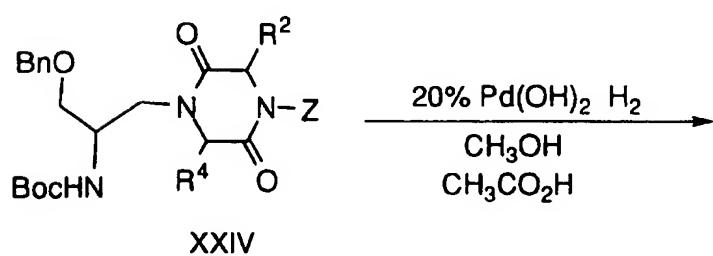
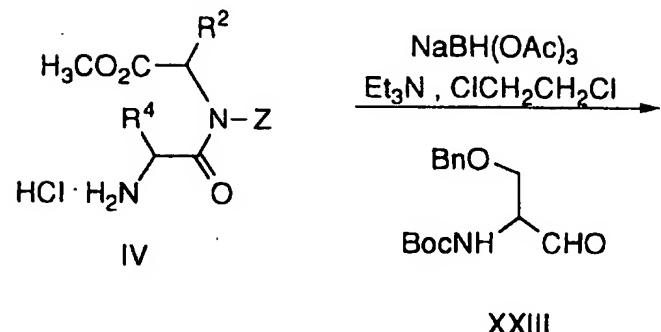
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SCHEME 3b



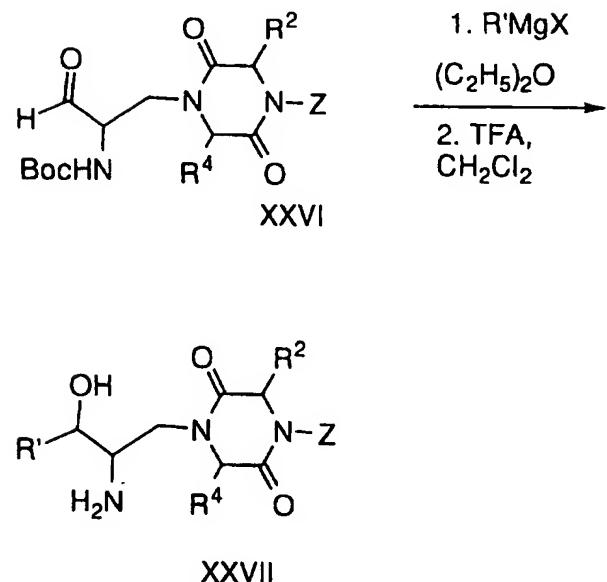
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SCHEME 4



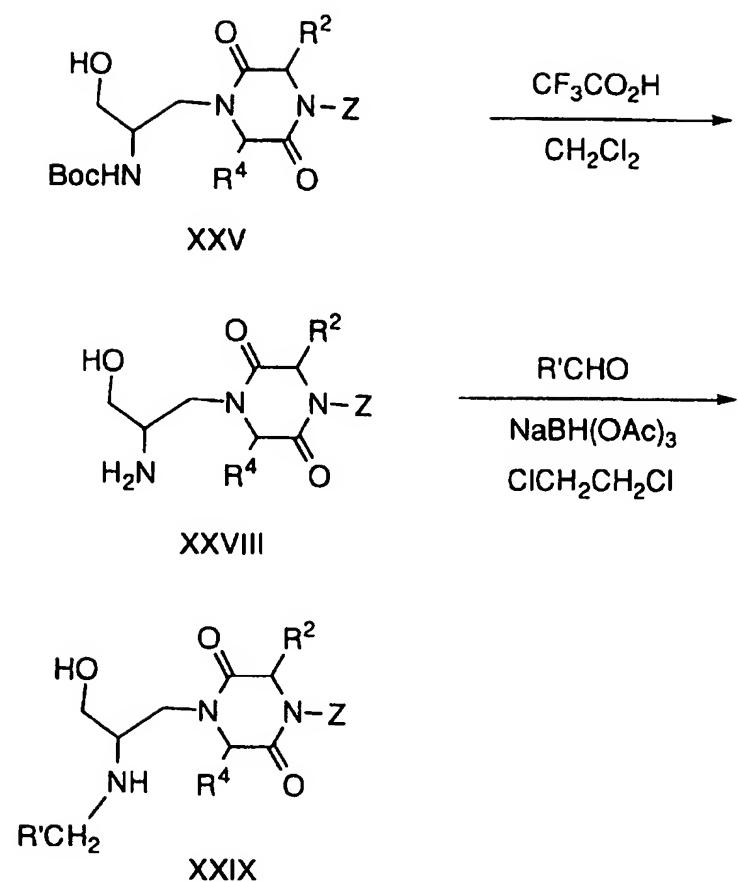
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SCHEME 4 (CONTINUED)



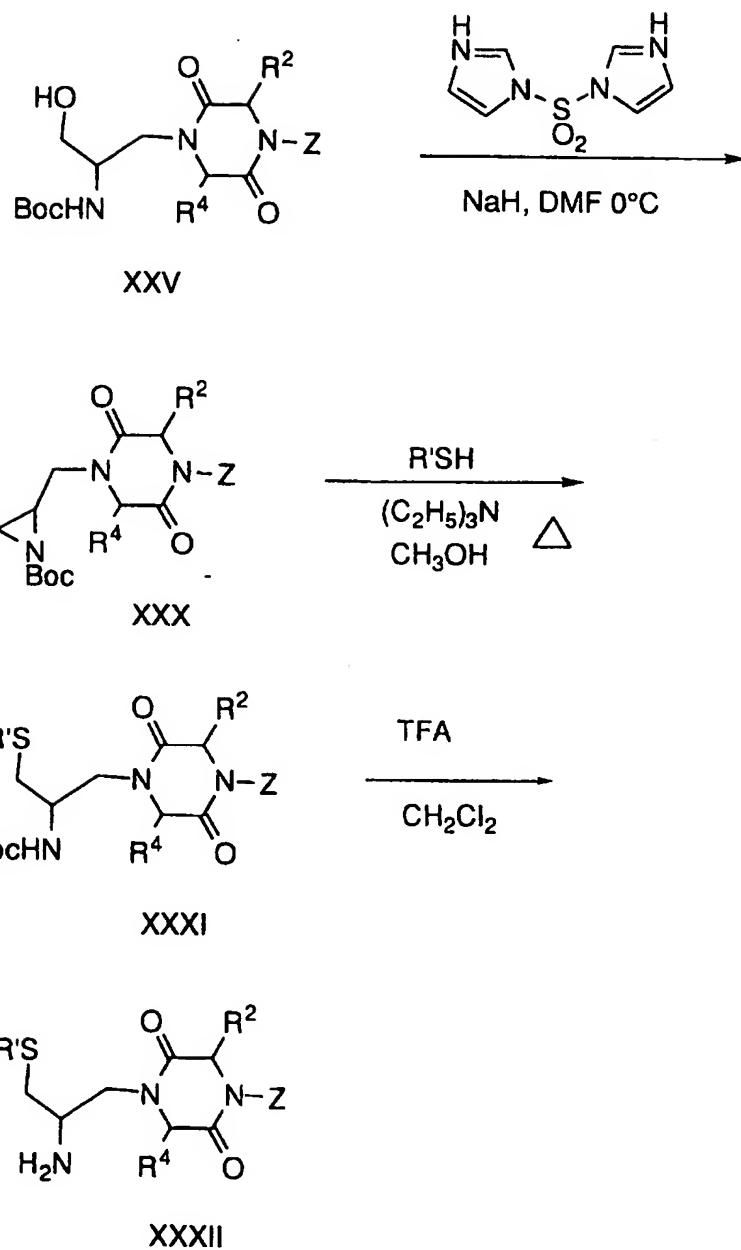
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SCHEME 5



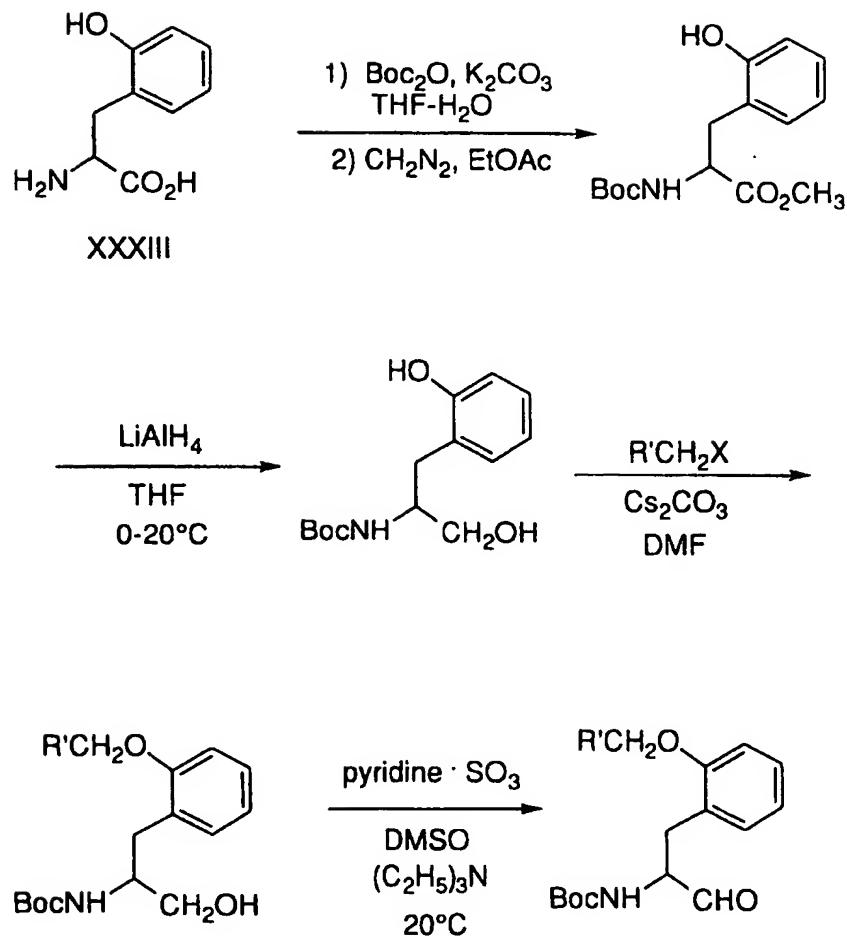
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SCHEME 6



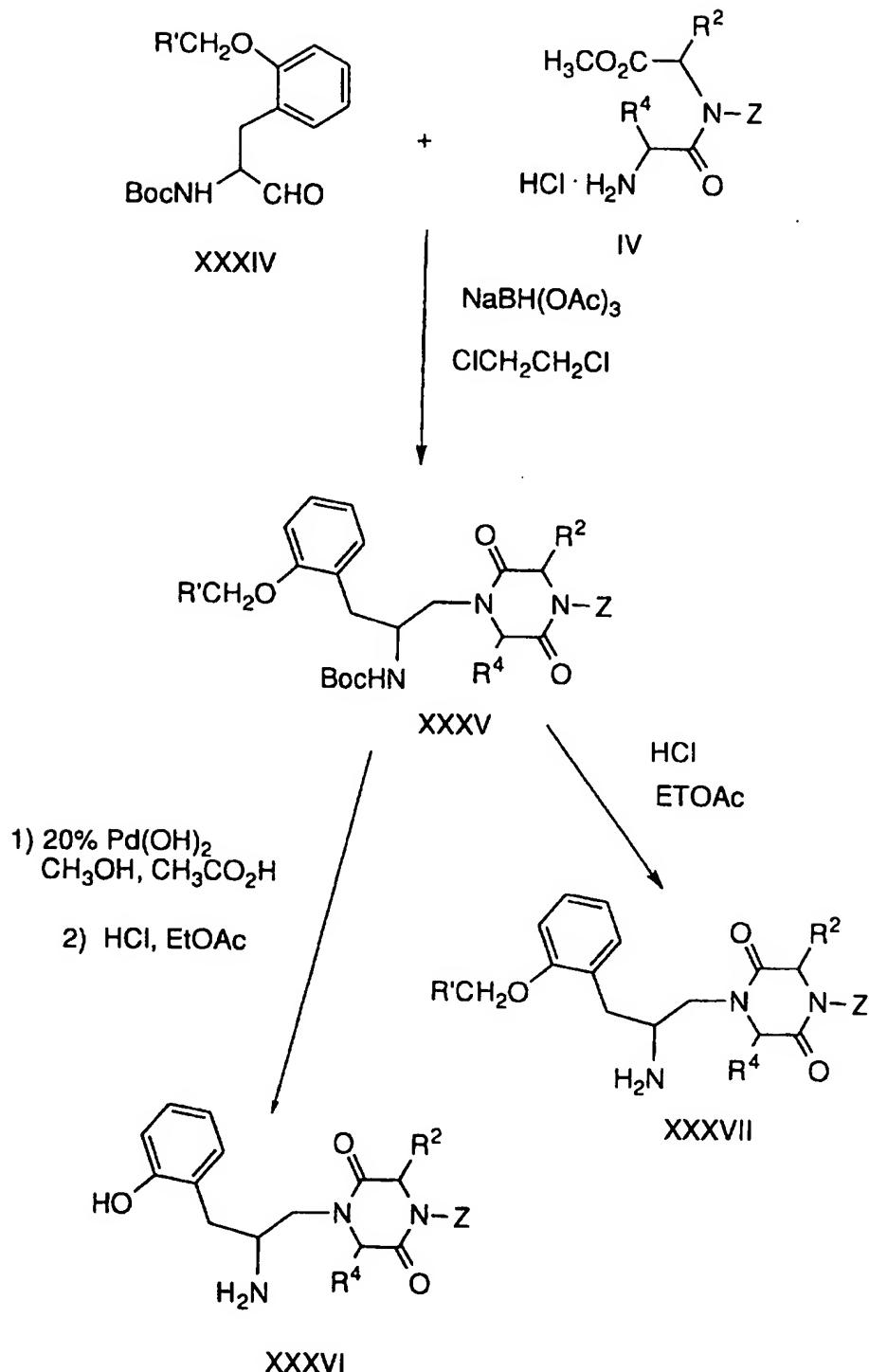
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SCHEME 7



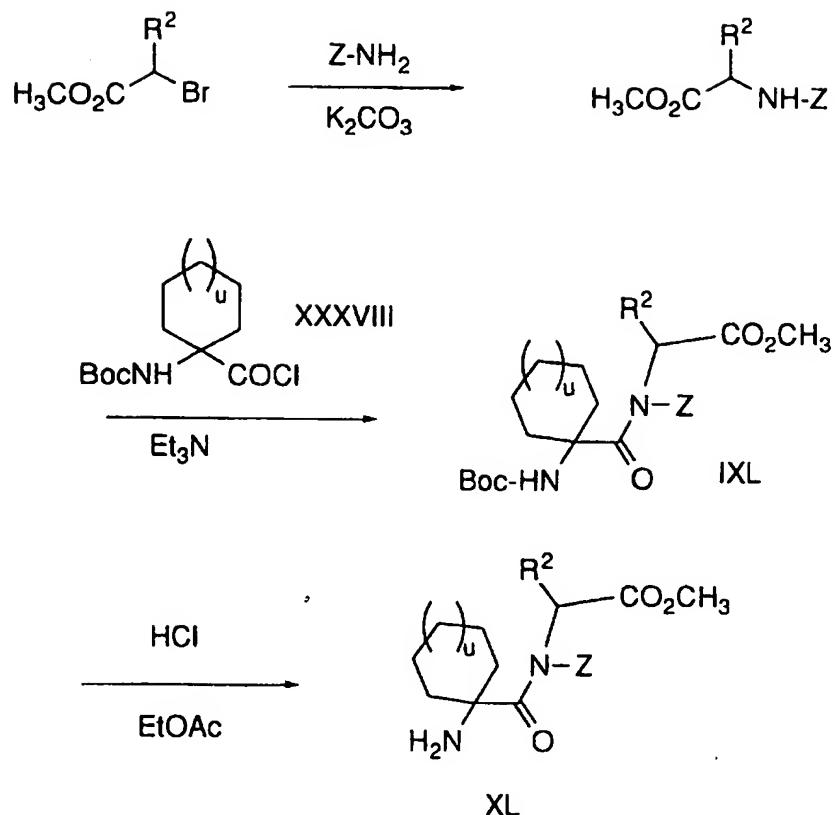
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SCHEME 7 (continued)



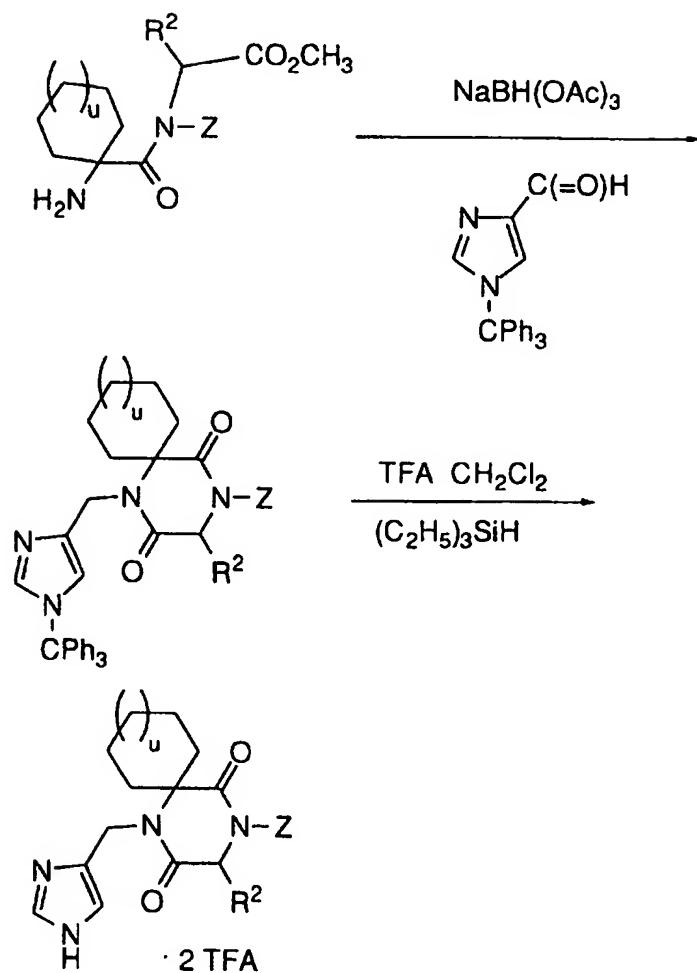
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SCHEME 8



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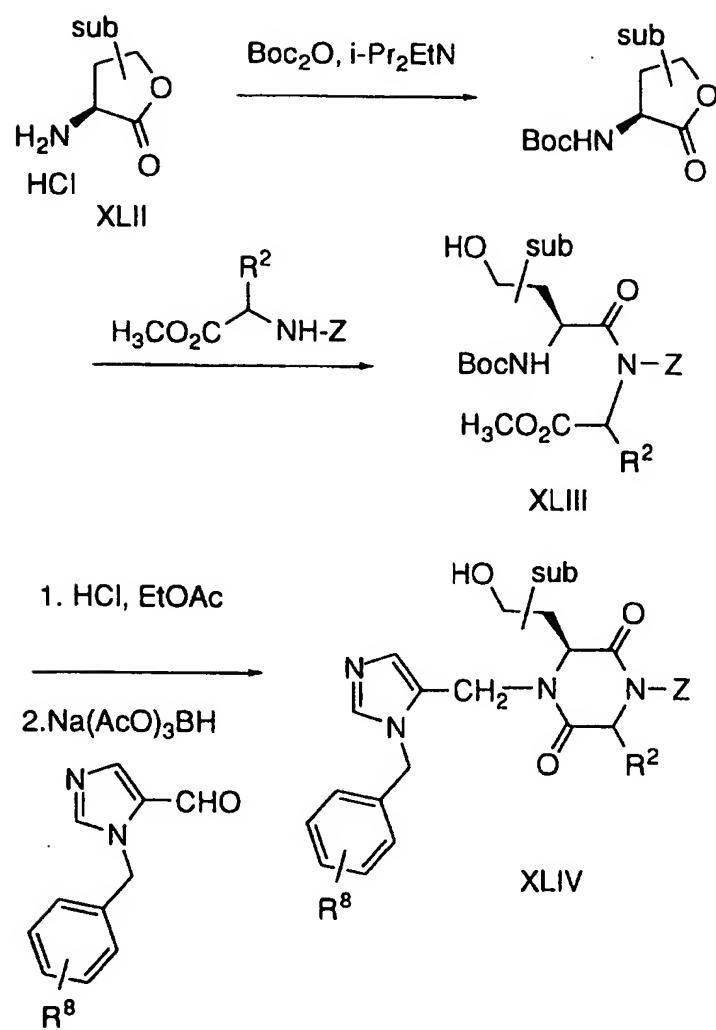
SCHEME 8 (continued)



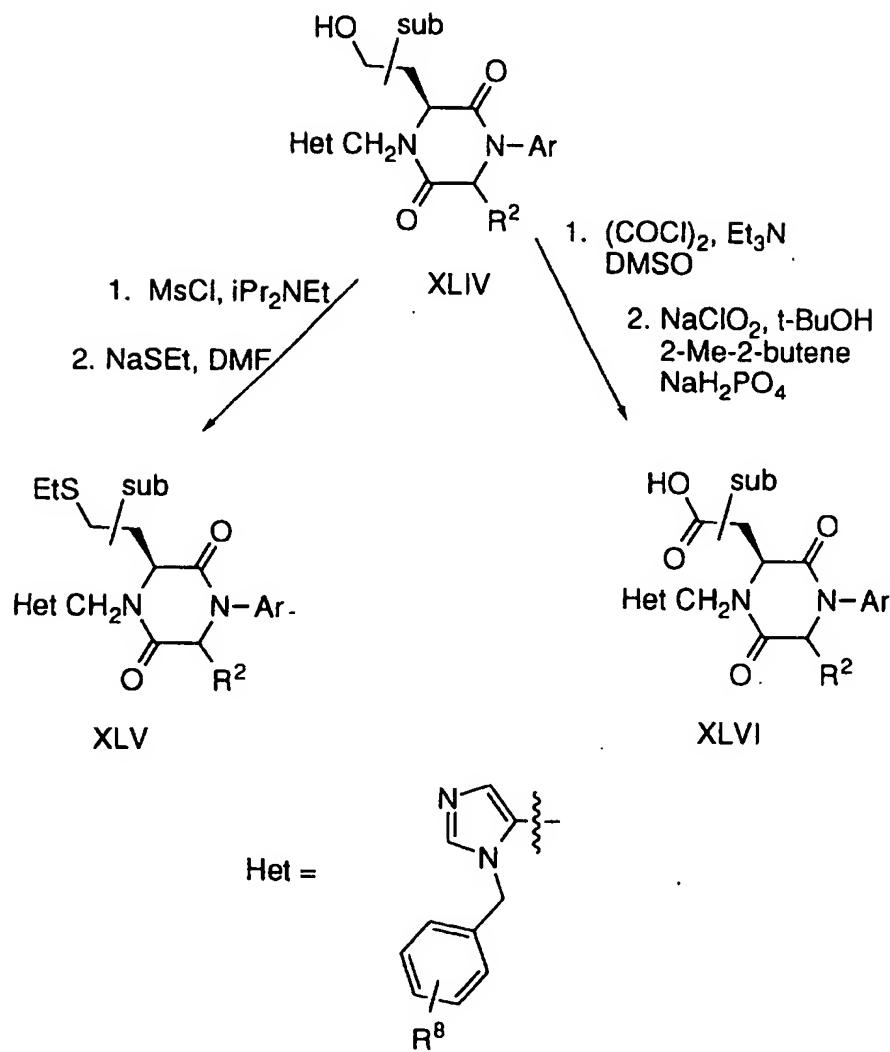
XLI

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SCHEME 9

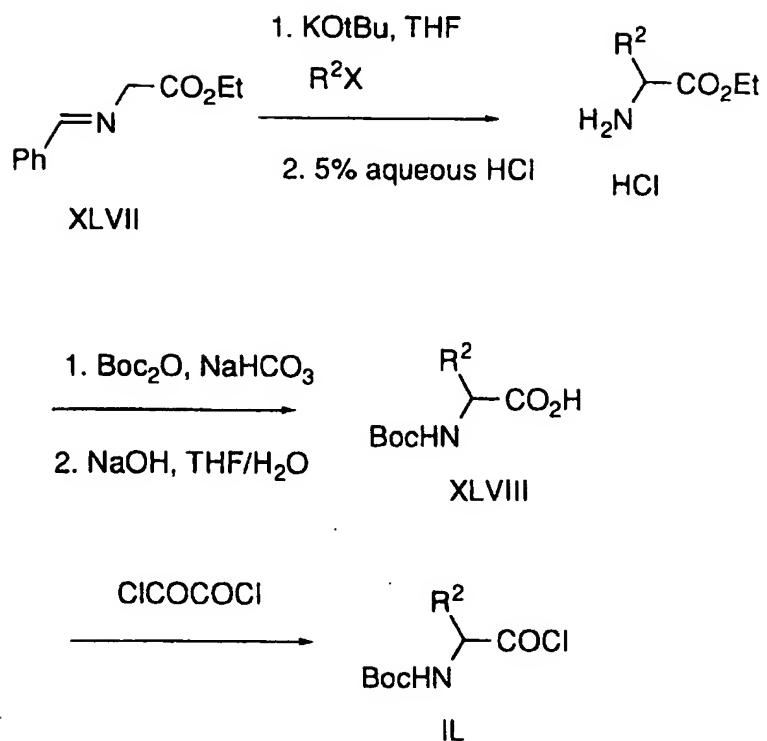


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SCHEME 9 (continued)

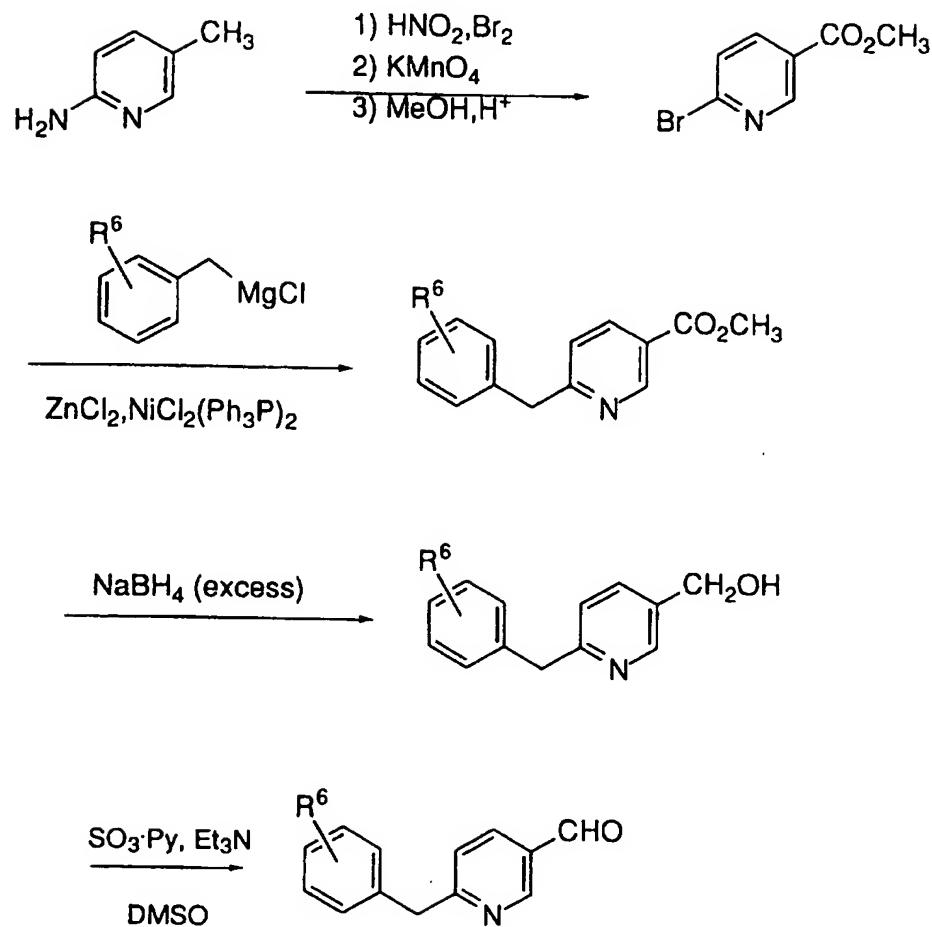
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SCHEME 10



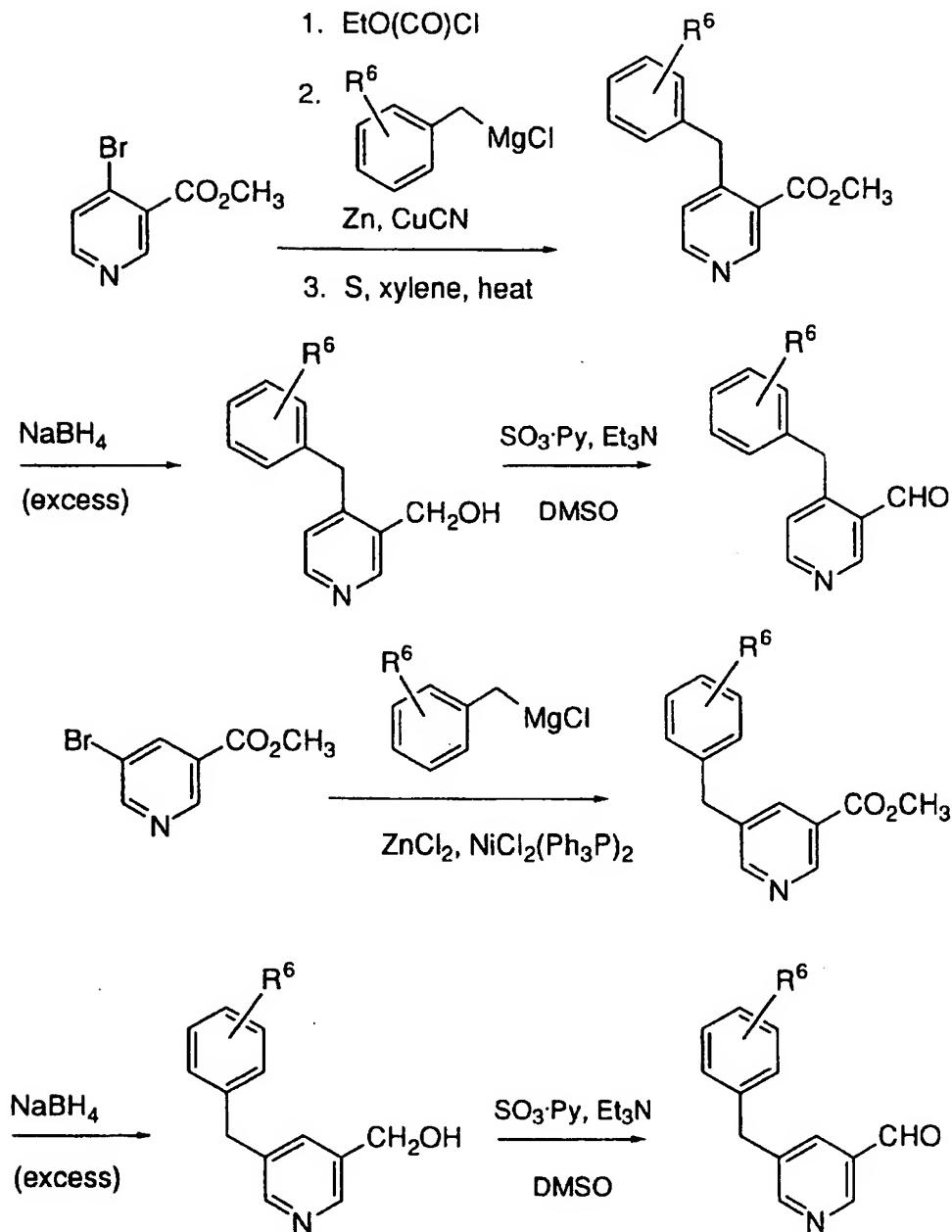
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REACTION SCHEME 11



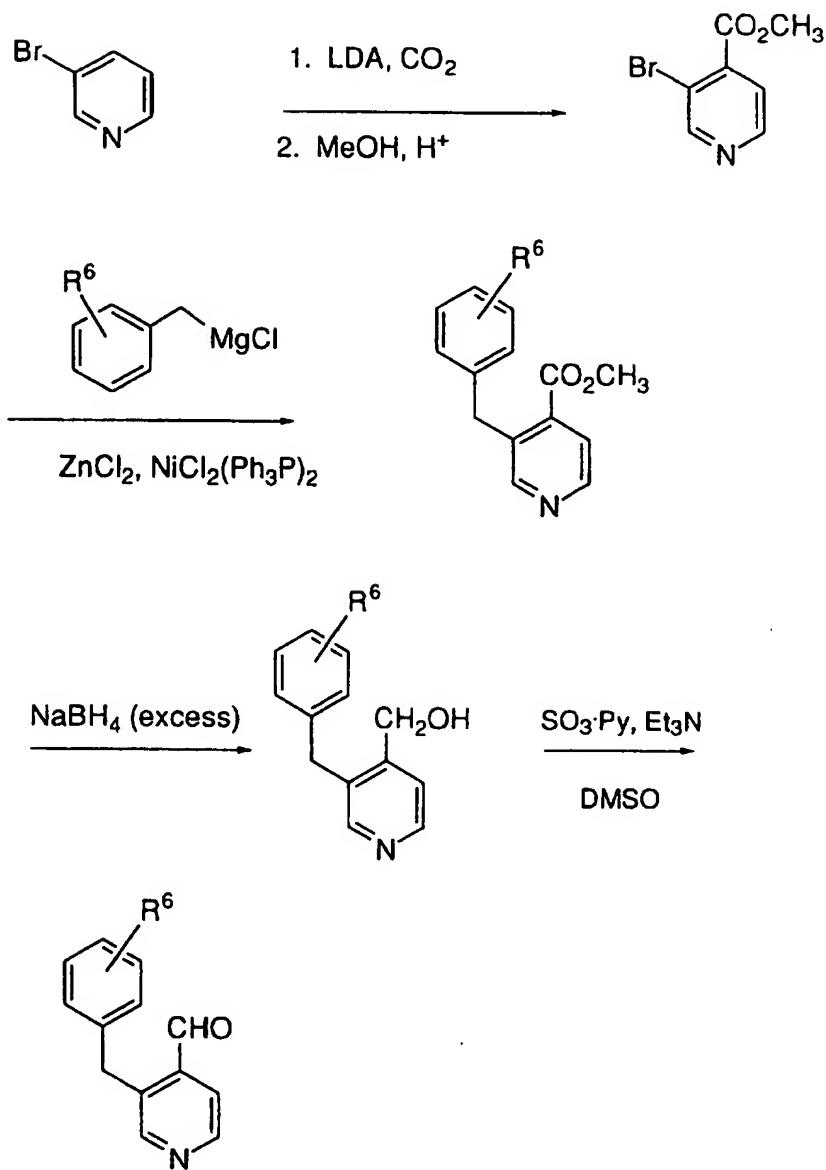
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REACTION SCHEME 12



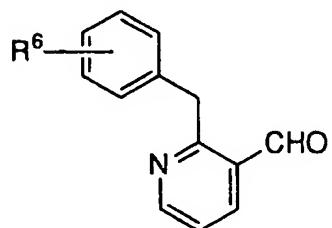
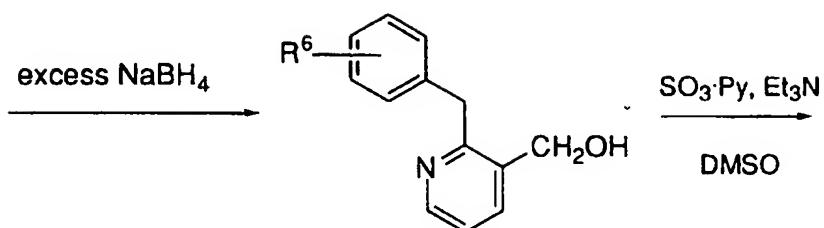
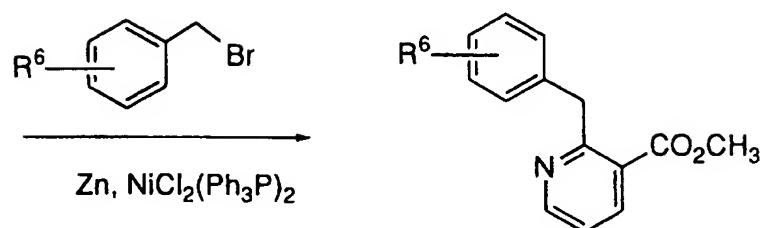
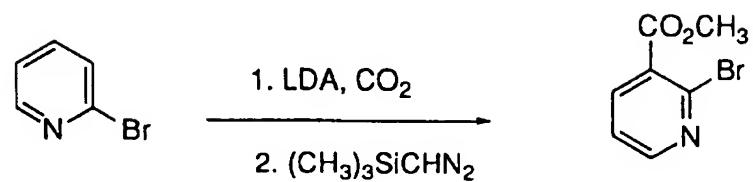
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REACTION SCHEME 13



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REACTION SCHEME 14



The instant compounds are useful as pharmaceutical agents for mammals, especially for humans. These compounds may be administered to patients for use in the treatment of cancer. Examples of the type of cancer which may be treated with the compounds of this invention include, but are not limited to, colorectal carcinoma, exocrine pancreatic carcinoma, myeloid leukemias and neurological tumors. Such tumors may arise by mutations in the *ras* genes themselves, mutations in the proteins that can regulate Ras activity (i.e., neurofibromin (NF-1), neu, scr, abl, lck, fyn) or by other mechanisms.

5 The compounds of the instant invention inhibit farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. The instant compounds may also inhibit tumor angiogenesis, thereby affecting the growth of tumors (J. Rak et al. *Cancer Research*, 55:4575-4580 (1995)). Such anti-angiogenesis properties of the instant
10 compounds may also be useful in the treatment of certain forms of blindness related to retinal vascularization.

15 The compounds of this invention are also useful for inhibiting other proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes (i.e., the Ras gene itself is not activated by mutation to an oncogenic form) with said inhibition being accomplished by the administration of an effective amount of the compounds of the invention to a mammal in need of such treatment. For example, a component of NF-1 is a benign proliferative disorder.

20 The instant compounds may also be useful in the treatment of certain viral infections, in particular in the treatment of hepatitis delta and related viruses (J.S. Glenn et al. *Science*, 256:1331-1333 (1992)).

25 The compounds of the instant invention are also useful in the prevention of restenosis after percutaneous transluminal coronary angioplasty by inhibiting neointimal formation (C. Indolfi et al. *Nature medicine*, 1:541-545(1995)).

30 The instant compounds may also be useful in the treatment and prevention of polycystic kidney disease (D.L. Schaffner et al.

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American Journal of Pathology, 142:1051-1060 (1993) and B. Cowley, Jr. et al.*FASEB Journal*, 2:A3160 (1988)).

The instant compounds may also be useful for the treatment of fungal infections.

5 The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The
10 compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use of a chemotherapeutic compound according to this invention, the selected compound may be administered, for
15 example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried
20 corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH
25 of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The compounds of the instant invention may also be co-administered with other well known therapeutic agents that are selected
30 for their particular usefulness against the condition that is being treated. For example, the instant compounds may be useful in combination with known anti-cancer and cytotoxic agents. Similarly, the instant compounds may be useful in combination with agents that are effective in the treatment and prevention of NF-1, retinosis, polycystic kidney

disease, infections of hepatitis delta and related viruses and fungal infections.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range

5 described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

The present invention also encompasses a pharmaceutical 10 composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous 15 solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's blood-stream by local bolus injection.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be 20 determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for 25 cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The compounds of the instant invention are also useful 30 as a component in an assay to rapidly determine the presence and quantity of farnesyl-protein transferase (FPTase) in a composition. Thus the composition to be tested may be divided and the two portions contacted with mixtures which comprise a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine

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terminus) and farnesyl pyrophosphate and, in one of the mixtures, a compound of the instant invention. After the assay mixtures are incubated for an sufficient period of time, well known in the art, to allow the FPTase to farnesylyate the substrate, the chemical content of
5 the assay mixtures may be determined by well known immunological, radiochemical or chromatographic techniques. Because the compounds of the instant invention are selective inhibitors of FPTase, absence or quantitative reduction of the amount of substrate in the assay mixture without the compound of the instant
10 invention relative to the presence of the unchanged substrate in the assay containing the instant compound is indicative of the presence of FPTase in the composition to be tested.

It would be readily apparent to one of ordinary skill in the art that such an assay as described above would be useful in identifying
15 tissue samples which contain farnesyl-protein transferase and quantitating the enzyme. Thus, potent inhibitor compounds of the instant invention may be used in an active site titration assay to determine the quantity of enzyme in the sample. A series of samples composed of aliquots of a tissue extract containing an unknown amount
20 of farnesyl-protein transferase, an excess amount of a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate are incubated for an appropriate period of time in the presence of varying concentrations of a compound of the instant invention. The concentration of a sufficiently potent
25 inhibitor (i.e., one that has a K_i substantially smaller than the concentration of enzyme in the assay vessel) required to inhibit the enzymatic activity of the sample by 50% is approximately equal to half of the concentration of the enzyme in that particular sample.

30

EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species

and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof. Purification by HPLC was accomplished with a 40 X 100 mm Waters PrepPak® reverse phase HPLC column (Delta-Pak™ C₁₈ 15 µm, 100 Å). Gradient elution 5 employed 0.1% trifluoroacetic acid in water (Solvent A) and 0.1% trifluoroacetic acid in acetonitrile (Solvent B). Chloride salts were obtained by passing an aqueous solution of the trifluoroacetic acid salt through a Biorad AG® 3X4 ion exchange resin column (100-200 mesh, C1-form). Purification by HPLC was utilized for each of the Examples 10 1, and 49 as set forth below.

EXAMPLE 1

15 4-[1-(4-Cyanobenzyl)-5-imidazolylmethyl]-1-(3-chlorophenyl)-
piperazine-2,5-dione hydrochloride

Step A: Preparation of 1-triphenylmethyl-4-(hydroxymethyl)-
imidazole

20 To a solution of 4-(hydroxymethyl)imidazole hydrochloride (35.0 g, 260 mmol) in 250 mL of dry DMF at room temperature was added triethylamine (90.6 mL, 650 mmol). A white solid precipitated from the solution. Chlorotriphenylmethane (76.1 g, 273 mmol) in 500 mL of DMF was added dropwise. The reaction mixture was stirred for 20 hours, poured over ice, filtered, and washed 25 with ice water. The resulting product was slurried with cold dioxane, filtered, and dried *in vacuo* to provide the titled product as a white solid which was sufficiently pure for use in the next step.

30 Step B: Preparation of 1-triphenylmethyl-4-(acetoxymethyl)-
imidazole

Alcohol from Step A (260 mmol, prepared above) was suspended in 500 mL of pyridine. Acetic anhydride (74 mL, 780 mmol) was added dropwise, and the reaction was stirred for 48 hours during which it became homogeneous. The solution was poured into 2

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L of EtOAc, washed with water (3 x 1 L), 5% aq. HCl soln. (2 x 1 L), sat. aq. NaHCO₃, and brine, then dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the crude product. The acetate was isolated as a white powder (85.8 g, 86% yield for two steps) which was 5 sufficiently pure for use in the next reaction.

Step C: Preparation of 1-(4-cyanobenzyl)-5-(acetoxymethyl)-imidazole hydrobromide

A solution of the product from Step B (85.8 g, 225 mmol) 10 and α-bromo-*p*-tolunitrile (50.1 g, 232 mmol) in 500 mL of EtOAc was stirred at 60 °C for 20 hours, during which a pale yellow precipitate formed. The reaction was cooled to room temperature and filtered to provide the solid imidazolium bromide salt. The filtrate was concentrated *in vacuo* to a volume 200 mL, reheated at 60 °C for two 15 hours, cooled to room temperature, and filtered again. The filtrate was concentrated *in vacuo* to a volume 100 mL, reheated at 60 °C for another two hours, cooled to room temperature, and concentrated *in vacuo* to provide a pale yellow solid. All of the solid material was combined, dissolved in 500 mL of methanol, and warmed to 60 °C. 20 After two hours, the solution was reconcentrated *in vacuo* to provide a white solid which was triturated with hexane to remove soluble materials. Removal of residual solvents *in vacuo* provided the titled product hydrobromide as a white solid (50.4 g, 67% yield, 89% purity by HPLC) which was used in the next step without further purification.

25

Step D: Preparation of 1-(4-cyanobenzyl)-5-(hydroxymethyl)-imidazole

To a solution of the acetate from Step C (50.4 g, 150 mmol) in 1.5 L of 3:1 THF/water at 0 °C was added lithium hydroxide monohydrate (18.9 g, 450 mmol). After one hour, the reaction was 30 concentrated *in vacuo*, diluted with EtOAc (3 L), and washed with water, sat. aq. NaHCO₃ and brine. The solution was then dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the crude

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product (26.2 g, 82% yield) as a pale yellow fluffy solid which was sufficiently pure for use in the next step without further purification.

5 Step E: Preparation of 1-(4-cyanobenzyl)-5-imidazole-carboxaldehyde

To a solution of the alcohol from Step D (21.5 g, 101 mmol) in 500 mL of DMSO at room temperature was added triethylamine (56 mL, 402 mmol), then SO₃-pyridine complex (40.5 g, 254 mmol). After 45 minutes, the reaction was poured into 2.5 L of

10 EtOAc, washed with water (4 x 1 L) and brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the aldehyde (18.7 g, 88% yield) as a white powder which was sufficiently pure for use in the next step without further purification.

15 Step F: Preparation of methyl 2-[(3-chlorophenyl)amino]acetate

To a solution of 3-chloroaniline and potassium carbonate (3 equiv.) in DMF is added methylbromoacetate (1.1 equiv.), and the reaction is stirred at 60 °C. After complete reaction, the solution is

20 poured into EtOAc and washed with water, sat. aq. NaHCO₃ soln., and brine. The solution is dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The resulting material is purified by silica gel chromatography to provide the titled compound.

25 Step G: Preparation of 2-[(*tert*-butoxycarbonyl)amino]-N-(3-chlorophenyl)-N-[(carbomethoxy)methyl]acetamide

To a solution of Boc-glycine and triethylamine (1.0 equiv.) in dichloromethane at 0 °C is added oxalylchloride (1.0 equiv.). After one hour, a solution of the product from Step F (1 equiv.) in dichloromethane is added to the first solution, followed by triethylamine (1 equiv.). The solution is allowed to warm to room temperature.

30 After complete reaction, the solution is poured into EtOAc and washed with sat. NH₄Cl soln., sat. NaHCO₃ soln., and brine. The solution is dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The resulting

- 64 -

material is purified by silica gel chromatography to provide the titled compound.

Step H: Preparation of 2-amino-N-(3-chlorophenyl)-N-[(carbomethoxy)methyl]acetamide

5 Through a solution of Boc-protected amine from Step G in EtOAc at 0 °C is bubbled anhydrous HCl gas. After the reaction is complete, nitrogen gas is bubbled through the reaction to remove excess HCl, and the mixture is warmed to room temperature. The solution is
10 concentrated *in vacuo* to provide the hydrochloride which is used in the next step without further purification.

Step I: Preparation of 4-[1-(4-cyanobenzyl)-5-imidazolymethyl]-1-(3-chlorophenyl)piperazine-2,5-dione hydrochloride

15 To a solution of the amine hydrochloride from Step H in 1,2-dichloroethane at 0 °C is added 4Å powdered molecular sieves (200 wt %), followed by sodium triacetoxyborohydride (1.5 equiv.). The aldehyde from Step E (1.1 equiv.) is added, and the reaction is stirred overnight, allowing it to warm to room temperature. After completion,
20 the reaction is poured into EtOAc, washed with sat. aq. NaHCO₃, and brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The resulting product is taken up in CH₂Cl₂, and propylamine (20 vol %) is added. The reaction is stirred for 12 hours, then concentrated *in vacuo*, and purified by silica gel chromatography. The resulting product is
25 taken up in CH₂Cl₂ and treated with excess 1 M HCl/ether solution, and concentrated *in vacuo* to provide the titled product hydrochloride.

EXAMPLE 2

30 (S)-3-*n*-Butyl-4-[1-(4-cyanobenzyl)-5-imidazolymethyl]-1-(3-chlorophenyl)piperazine-2,5-dione hydrochloride

The titled compound is prepared from the amine product from Step F of Example 1 using the reaction sequence described in Steps

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- G, H, and I of Example 1, except that in Step G the Boc-glycine is substituted with (S)-2-butoxycarbonylaminohexanoic acid. After the three Steps, the product is purified by silica gel chromatography, then taken up in CH₂Cl₂ and treated with excess 1 M HCl/ether solution, and concentrated *in vacuo* to provide the titled product hydrochloride.

EXAMPLE 3

- 10 1-(3-Chlorophenyl)-4-[(3-(4-cyanobenzyl)pyridin-4-yl)methyl]-piperazine-2,5-dione hydrochloride
-

Step A: Preparation of 3-(4-cyanobenzyl)pyridin-4-carboxylic acid methyl ester

- 15 A solution of 4-cyanobenzyl bromide (625 mg, 3.27 mmol) in dry THF (4mL) was added slowly over ~3 min. to a suspension of activated Zn (dust; 250 mg) in dry THF (2 mL) at 0° under an argon atmosphere. The ice-bath was removed and the slurry was stirred at room temperature for a further 30 min. Then 3-bromopyridin-4-carboxylic acid methyl ester (540 mg, 2.5 mmol) followed by
- 20 dichlorobis(triphenylphosphine)nickel (II) (50 mg). The resultant reddish-brown mixture was stirred for 3h at ~40-45°C. The mixture was cooled and distributed between EtOAc (100 ml) and 5% aqueous citric acid (50 mL). The organic layer was washed with H₂O (2X50 mL), dried with Na₂SO₄. After evaporation of the solvent the residue
- 25 was purified on silica gel, eluting with 35% EtOAc in hexane to give 420 mg as a clear gum. FAB ms (M+I) 253.

Step B: Preparation of 3-(4-cyanobenzyl)-4-(hydroxymethyl)-pyridine

- 30 The title compound was obtained by sodium borohydride (300 mg) reduction of the ester from Step A (415 mg) in methanol (5 mL) at room temperature. After stirring for 4 h the solution was evaporated and the product was purified on silica gel, eluting with 2%

- 66 -

methanol in chloroform to give the title compound. FAB ms (M+1) 225.

Step C: Preparation of 3-(4-cyanobenzyl)-4-pyridinal

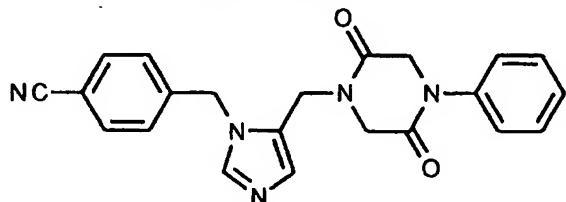
5 The title compound was obtained by activated manganese dioxide (1.0g) oxidation of the alcohol from Step B (240 mg, 1.07 mmol) in dioxane (10 mL) at reflux for 30 min. Filtration and evaporation of the solvent provided title compound, mp 80-83°C.

10 **Step D: Preparation of 1-(3-chlorophenyl)-4-[(3-(4-cyanobenzyl)pyridin-4-yl)methyl]-piperazine-2,5-dione hydrochloride**

15 The titled compound is prepared from the pyridinal from Step C and the amine hydrochloride from Step H of Example 1 using the reductive alkylation procedure in Step I of Example 1. The product is purified by silica gel chromatography, then taken up in CH₂Cl₂ and treated with excess 1 M HCl/ether solution, and concentrated *in vacuo* to provide the titled product hydrochloride.

20

EXAMPLE 4



4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-phenylpiperazine-2,5-dione hydrochloride

25 **Step A: Preparation of 1-(4-cyanobenzyl)-5-[N-((carbomethoxy)methyl)aminomethyl]-imidazole**

To a solution of glycine methyl ester hydrochloride (595 mg, 4.74 mmol) in 1,2-dichloroethane at 0 °C was added 4 Å powdered molecular sieves (3g), followed by sodium 30 triacetoxyborohydride (1.51 g, 7.1 mmol). The 1-(4-cyanobenzyl)-

5-imidazolecarboxaldehyde from Step E of Example 1 (1.00 g, 4.74 mmol) was added, and the reaction was stirred overnight, allowing it to warm to room temperature. The reaction was poured into EtOAc, washed with sat. aq. NaHCO₃, and brine, dried (Na₂SO₄), filtered,

5 and concentrated *in vacuo*. The resulting product was taken up in CH₂Cl₂, and propylamine (20 vol %) was added. The reaction was stirred for one hour, then concentrated *in vacuo*, and purified by silica gel chromatography (95:5; CHCl₃:MeOH) to provide the titled amine product.

10

Step B: Preparation of 1-(4-cyanobenzyl)-5-[N-((carbomethoxy)-methyl)-N-(2-((*tert*-butoxycarbonyl)-amino)acetamido)aminomethyl]imidazole

To a solution of the product of Step A (750 mg, 2.64 mmol) and Boc-glycine (462 mg, 2.64 mmol) in 10 mL of DMF was added HOBr•H₂O (392 mg, 2.9 mmol) and EDC•HCl (556 mg, 2.9 mmol). The reaction was stirred at room temperature for 2.5 hours. The solution was poured into EtOAc and washed with sat. aq. NaHCO₃ soln., and brine, then dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The resulting titled product was used in the next step without further purification.

25

Step C: Preparation of 1-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-piperazine-2,5-dione

Through a solution of Boc-protected amine from Step B (930 mg, 2.1 mmol) in 10 mL of EtOAc at 0 °C was bubbled anhydrous HCl gas. After 30 minutes the solution was concentrated *in vacuo* to provide a solid hydrochloride salt. This was taken up in dichloromethane (25 mL), and triethylamine was added (0.725 mL, 5.2 mmol). After stirring for 2 hours, the solvent was removed *in vacuo*, and the resulting residue taken up in EtOAc/EtOH. The solution was washed with sat. aq. NaHCO₃ soln., and brine, then dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The resulting titled product was used in the next step without further purification.

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Step D: Preparation of 4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-phenylpiperazine-2,5-dione hydrochloride

5 A mixture of the product from Step C (309 mg, 1.0 mmol), triphenylbismuth (660 mg, 1.5 mmol), triethylamine (0.209 mL, 1.5 mmol), and copper(II) acetate (272 mg, 1.5 mmol) was stirred together in 7 mL of dichloromethane. After 18 hours, the solution was added to a silica gel chromatography column, and eluted
 10 with 3%-7% MeOH/CHCl₃ solution. The resulting product was treated with excess 1 M HCl/ether solution, and concentrated *in vacuo* to provide the titled product hydrochloride as a white solid.

FAB mass spectrum m/e 386.14 (M+1).

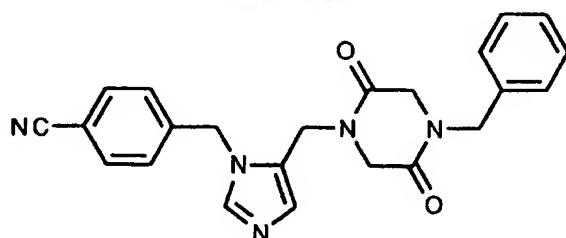
15 Analysis calculated for C₂₂H₁₉N₅O₂ • 1.0 HCl • 0.15 H₂O • 0.45 CHCl₃:

C, 56.38; H, 4.37; N, 14.64;

Found: C, 56.36; H, 4.39; N, 14.54.

20

EXAMPLE 5



4-benzyl-1-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-piperazine-2,5-dione hydrochloride

25 To a solution of the diketopiperazine product from Step C of Example 4 (41 mg, 0.13 mmol) and benzylbromide (0.017 mL, 0.14 mmol) in 2.0 mL of DMF was added at room temperature sodium hydride (5 mg, 60% dispersion in mineral oil). After 2 hours, the solution was diluted with EtOAc and washed with sat. aq. NaHCO₃ soln., and brine, then dried (Na₂SO₄), filtered, and
 30 concentrated *in vacuo*. The crude product was purified by

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preparative silica gel TLC using 10% MeOH/CHCl₃ as solvent. The resulting product was treated with excess 1 M HCl/ether solution, and concentrated *in vacuo* to provide the titled product hydrochloride as a white solid.

5

FAB mass spectrum m/e 400.05 (M+1).

Analysis calculated for C₂₃H₂₁N₅O₂ • 1.0 HCl • 1.00 MeOH • 0.40 CHCl₃:

10 Found: C, 56.83; H, 5.16; N, 13.58;
 C, 56.81; H, 5.03; N, 13.07.

EXAMPLE 6

In vitro inhibition of ras farnesyl transferase

15 Assays of farnesyl-protein transferase. Partially purified bovine FPTase and Ras peptides (Ras-CVLS, Ras-CVIM and Ras-CAIL) were prepared as described by Schaber *et al.*, *J. Biol. Chem.* 265:14701-14704 (1990), Pompliano, *et al.*, *Biochemistry* 31:3800 (1992) and Gibbs *et al.*, *PNAS U.S.A.* 86:6630-6634 (1989), respectively. Bovine
20 FPTase was assayed in a volume of 100 µl containing 100 mM N-(2-hydroxy ethyl) piperazine-N'-(2-ethane sulfonic acid) (HEPES), pH 7.4, 5 mM MgCl₂, 5 mM dithiothreitol (DTT), 100 mM [³H]-farnesyl diphosphate ([³H]-FPP; 740 CBq/mmol, New England Nuclear), 650 nM Ras-CVLS and 10 µg/ml FPTase at 31°C for 60 min. Reactions were
25 initiated with FPTase and stopped with 1 ml of 1.0 M HCl in ethanol. Precipitates were collected onto filter-mats using a TomTec Mach II cell harvester, washed with 100% ethanol, dried and counted in an LKB β-plate counter. The assay was linear with respect to both substrates, FPTase levels and time; less than 10% of the [³H]-FPP was utilized
30 during the reaction period. Purified compounds were dissolved in 100% dimethyl sulfoxide (DMSO) and were diluted 20-fold into the assay. Percentage inhibition is measured by the amount of incorporation of radioactivity in the presence of the test compound

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when compared to the amount of incorporation in the absence of the test compound.

- Human FPTase was prepared as described by Omer *et al.*, Biochemistry 32:5167-5176 (1993). Human FPTase activity was assayed as described above with the exception that 0.1% (w/v) polyethylene glycol 20,000, 10 µM ZnCl₂ and 100 nm Ras-CVIM were added to the reaction mixture. Reactions were performed for 30 min., stopped with 100 µl of 30% (v/v) trichloroacetic acid (TCA) in ethanol and processed as described above for the bovine enzyme.
- The compounds of the instant invention described in the Examples 4 and 5 were tested for inhibitory activity against human FPTase by the assay described above and were found to have IC₅₀ of ≤ 50 µM.

15

EXAMPLE 5

In vivo ras farnesylation assay

- The cell line used in this assay is a v-ras line derived from either Rat1 or NIH3T3 cells, which expressed viral Ha-ras p21. The assay is performed essentially as described in DeClue, J.E. *et al.*, Cancer Research 51:712-717, (1991). Cells in 10 cm dishes at 50-75% confluence are treated with the test compound (final concentration of solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C, the cells are labelled in 3 ml methionine-free DMEM supplemented with 10% regular DMEM, 2% fetal bovine serum and 400 mCi[³⁵S]methionine (1000 Ci/mmol). After an additional 20 hours, the cells are lysed in 1 ml lysis buffer (1% NP40/20 mM HEPES, pH 7.5/5 mM MgCl₂/1mM DTT/10 mg/ml aprotinin/2 mg/ml leupeptin/2 mg/ml antipain/0.5 mM PMSF) and the lysates cleared by centrifugation at 100,000 x g for 45 min. Aliquots of lysates containing equal numbers of acid-precipitable counts are brought to 1 ml with IP buffer (lysis buffer lacking DTT) and immunoprecipitated with the ras-specific monoclonal antibody Y13-259 (Furth, M.E. *et al.*, J. Virol. 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 ml of a

- 71 -

25% suspension of protein A-Sepharose coated with rabbit anti rat IgG is added for 45 min. The immunoprecipitates are washed four times with IP buffer (20 nM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100/0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE sample buffer and loaded on 13% acrylamide gels. When the dye front reached the bottom, the gel is fixed, soaked in Enlightening, dried and autoradiographed. The intensities of the bands corresponding to farnesylated and nonfarnesylated ras proteins are compared to determine the percent inhibition of farnesyl transfer to protein.

10

EXAMPLE 6

In vivo growth inhibition assay

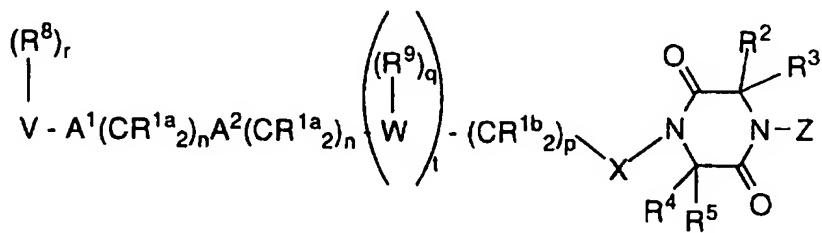
To determine the biological consequences of FPTase inhibition, the effect of the compounds of the instant invention on the anchorage-independent growth of Rat1 cells transformed with either a v-ras, v-raf, or v-mos oncogene is tested. Cells transformed by v-Raf and v-Mos maybe included in the analysis to evaluate the specificity of instant compounds for Ras-induced cell transformation.

Rat 1 cells transformed with either v-ras, v-raf, or v-mos are seeded at a density of 1×10^4 cells per plate (35 mm in diameter) in a 0.3% top agarose layer in medium A (Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum) over a bottom agarose layer (0.6%). Both layers contain 0.1% methanol or an appropriate concentration of the instant compound (dissolved in methanol at 1000 times the final concentration used in the assay). The cells are fed twice weekly with 0.5 ml of medium A containing 0.1% methanol or the concentration of the instant compound. Photomicrographs are taken 16 days after the cultures are seeded and comparisons are made.

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WHAT IS CLAIMED IS:

1. A compound which inhibits farnesyl-protein transferase of the formula A:



5

A

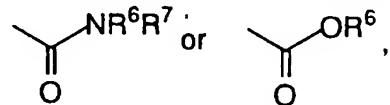
wherein:

R^{1a} and R^{1b} are independently selected from:

- a) hydrogen,
- 10 b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) unsubstituted or substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, and R¹¹OC(O)-NR¹⁰-,
- 15
- 20

R² and R⁴ are independently selected from: H; unsubstituted or substituted C₁-8 alkyl, unsubstituted or substituted C₂-8 alkenyl, unsubstituted or substituted C₂-8 alkynyl, unsubstituted or substituted aryl,

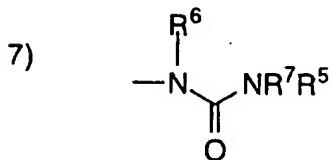
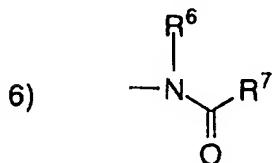
- 25 unsubstituted or substituted heterocycle,



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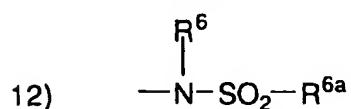
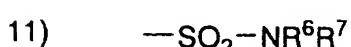
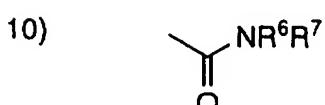
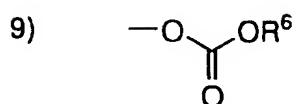
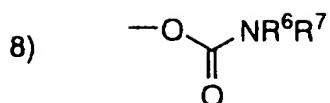
wherein the substituted group is substituted with one or more of:

- 5 1) aryl or heterocycle, unsubstituted or substituted with:
 a) C₁-4 alkyl,
 b) (CH₂)_pOR⁶,
 c) (CH₂)_pNR⁶R⁷,
 d) halogen,
 e) CN,
 f) aryl or heteroaryl,
 g) perfluoro-C₁-4 alkyl, or
 h) SR^{6a}, S(O)R^{6a}, SO₂R^{6a},
- 10 2) C₃-6 cycloalkyl,
 3) OR⁶,
 4) SR^{6a}, S(O)R^{6a}, or SO₂R^{6a},
- 5) —NR⁶R⁷



15

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15) N₃.

16) F. or

17) perfluoro-C₁₋₄-alkyl;

5 R³ and R⁵ are selected from H and CH₃; or

R² and R³ or R⁴ and R⁵ attached to the same C atom are combined to form - (CH₂)_u - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR¹⁰)-;

10

R⁶, R⁷ and R^{7a} are independently selected from: H; C₁₋₄ alkyl, C₃₋₆ cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroaryl sulfonyl, unsubstituted or substituted with:

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- a) C1-4 alkoxy,
 - b) aryl or heterocycle,
 - c) halogen,
 - d) HO,

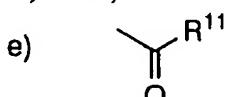


5 f) $\text{—SO}_2\text{R}^{11}$, or
g) $\text{N}(\text{R}^{10})_2$; or

R⁶ and R⁷ may be joined in a ring;
R⁷ and R^{7a} may be joined in a ring;

10 R^{6a} is selected from: C₁₋₄ alkyl, C₃₋₆ cycloalkyl, heterocycle, aryl, unsubstituted or substituted with:

- a) C₁-4 alkoxy,
 - b) aryl or heterocycle,
 - c) halogen,
 - d) HO.



f) $-\text{SO}_2\text{R}^{11}$, or
g) $\text{N}(\text{R}^{10})_2$:

20 R8 is independently selected from:

- a) hydrogen,
 - b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and C₁-C₆ alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
 - c)

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$R^{11}S(O)_m$ -, $R^{10}C(O)NH$ -, $(R^{10})_2NC(O)$ -, R^{10}_2N -
 $C(NR^{10})$ -, CN, $R^{10}C(O)$ -, N₃, -N(R^{10})₂, or
 $R^{10}OC(O)NH$;-;

5 R⁹ is selected from:

- a) hydrogen,
- b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$ -,
 $R^{11}S(O)_m$ -, $R^{10}C(O)NR^{10}$ -, $(R^{10})_2NC(O)$ -, R^{10}_2N -
 $C(NR^{10})$ -, CN, NO₂, $R^{10}C(O)$ -, N₃, -N(R^{10})₂, or
 $R^{11}OC(O)NR^{10}$ -, and
- c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl,
F, Cl, Br, $R^{10}O$ -, $R^{11}S(O)_m$ -, $R^{10}C(O)NR^{10}$ -,
 $(R^{10})_2NC(O)$ -, $R^{10}_2N-C(NR^{10})$ -, CN, $R^{10}C(O)$ -, N₃,
-N(R^{10})₂, or $R^{11}OC(O)NR^{10}$;-;

15

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

20

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-,
-C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R^{10})-,
-S(O)₂N(R^{10})-, -N(R^{10})S(O)₂-, or S(O)_m;

25 V is selected from:

- a) hydrogen,
- b) heterocycle,
- c) aryl,
- d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are
replaced with a heteroatom selected from O, S, and N,
and
- e) C₂-C₂₀ alkenyl,

provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen
if A¹ is a bond, n is 0 and A² is S(O)_m;

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W is a heterocycle;

X is a bond, -CH₂-, -C(=O)-, or -S(=O)_m-;

5

Z is selected from:

1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:

10

a) C₁-4 alkyl, unsubstituted or substituted with: C₁-4 alkoxy, NR⁶R⁷, C₃-6 cycloalkyl, aryl, heterocycle, HO, -S(O)_mR^{6a}, or -C(O)NR⁶R⁷,

15

b) aryl or heterocycle,

c) halogen,

d) OR⁶,

e) NR⁶R⁷,

f) CN,

g) NO₂,

20

h) CF₃;

i) -S(O)_mR^{6a},

j) -C(O)NR⁶R⁷, or

k) C₃-C₆ cycloalkyl; or

25

2) unsubstituted C₁-C₆ alkyl, substituted C₁-C₆ alkyl,

unsubstituted C₃-C₆ cycloalkyl or substituted C₃-C₆ cycloalkyl, wherein the substituted C₁-C₆ alkyl and substituted C₃-C₆ cycloalkyl is substituted with one or two of the following:

30

a) C₁-4 alkoxy,

b) NR⁶R⁷,

c) C₃-6 cycloalkyl,

d) -NR⁶C(O)R⁷,

e) HO,

f) -S(O)_mR^{6a},

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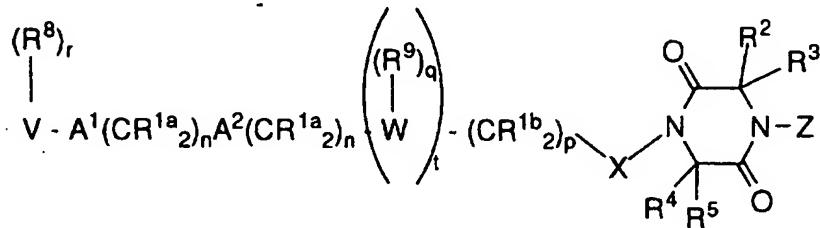
- g) halogen, or
- h) perfluoroalkyl;

	m is	0, 1 or 2;
5	n is	0, 1, 2, 3 or 4;
	p is	0, 1, 2, 3 or 4;
	q is	1 or 2;
	r is	0 to 5, provided that r is 0 when V is hydrogen;
	t is	0 or 1; and
10	u is	4 or 5;

or an optical isomer or pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1 of the formula A:

15



A

wherein:

R^{1a} is independently selected from: hydrogen or C₁-C₆ alkyl;

20

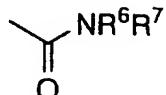
R^{1b} is independently selected from:

25

- a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, R¹⁰O-, -N(R¹⁰)₂ or C₂-C₆ alkenyl,
- c) unsubstituted or substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O- and -N(R¹⁰)₂;

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R³ and R⁵ are independently selected from H and CH₃;



R² and R⁴ are independently selected from H; alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

- 1) aryl,
- 2) heterocycle,
- 3) OR⁶,
- 4) SR^{6a}, SO₂R^{6a}, or
- 5)

10

R⁶, R⁷ and R^{7a} are independently selected from:

H; C₁-4 alkyl, C₃-6 cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

15

- a) C₁-4 alkoxy,
- b) halogen, or
- c) aryl or heterocycle;

R^{6a} is selected from:

20

C₁-4 alkyl or C₃-6 cycloalkyl, unsubstituted or substituted with:

- a) C₁-4 alkoxy,
- b) halogen, or
- c) aryl or heterocycle;

25

R⁸ is independently selected from:

30

- a) hydrogen,
- b) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and

- 80 -

- c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,

5 R⁹ is selected from:

- a) hydrogen,
b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or
10 R¹¹OC(O)NR¹⁰-, and
c) C₁-C₆ alkyl unsubstituted or substituted by C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,

15

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

20

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, O, -N(R¹⁰)-, or S(O)_m;

V is selected from:

- 25 a) hydrogen,
b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thieryl,
c) aryl,
30 d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
e) C₂-C₂₀ alkenyl, and

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provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl,

- 5 thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or isoquinolinyl;

X is -CH₂- or -C(=O)-;

10 Z is selected from:

- 1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:

15 a) C₁-4 alkyl, unsubstituted or substituted with: C₁-4 alkoxy, NR⁶R⁷, C₃-6 cycloalkyl, aryl, heterocycle, HO, -S(O)_mR^{6a}, or -C(O)NR⁶R⁷,

b) aryl or heterocycle,

c) halogen,

d) OR⁶,

e) NR⁶R⁷,

f) CN,

g) NO₂,

h) CF₃;

i) -S(O)_mR^{6a},

j) -C(O)NR⁶R⁷, or

k) C₃-C₆ cycloalkyl; or

- 2) unsubstituted C₁-C₆ alkyl, substituted C₁-C₆ alkyl, unsubstituted C₃-C₆ cycloalkyl or substituted C₃-C₆ cycloalkyl, wherein the substituted C₁-C₆ alkyl and substituted C₃-C₆ cycloalkyl is substituted with one or two of the following:

a) C₁-4 alkoxy,

b) NR⁶R⁷,

- 82 -

c) C₃-6 cycloalkyl,

d) -NR⁶C(O)R⁷,

e) HO,

f) -S(O)_mR^{6a},

5 g) halogen, or

h) perfluoroalkyl;

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

10 p is 0, 1, 2, 3 or 4;

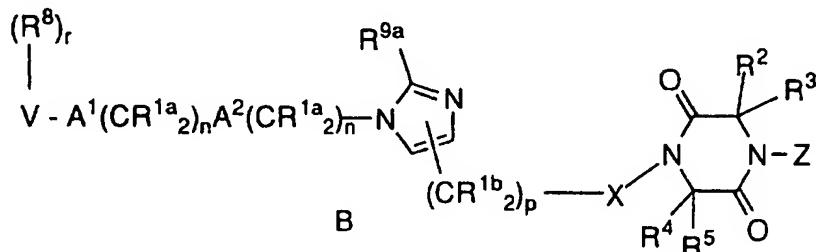
r is 0 to 5, provided that r is 0 when V is hydrogen;

t is 0 or 1; and

u is 4 or 5;

15 or a pharmaceutically acceptable salt thereof.

3. A compound according to Claim 1 of the formula B:



wherein:

20

R^{1a} is selected from: hydrogen or C₁-C₆ alkyl;

R^{1b} is independently selected from:

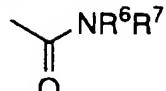
a) hydrogen,

25 b) aryl, heterocycle, cycloalkyl, R¹⁰O-, -N(R¹⁰)₂ or C₂-C₆ alkenyl,

c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, or -N(R¹⁰)₂;

- 83 -

R³ and R⁵ are independently selected from H and CH₃;



; or C₁₋₅

5 alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

- 1) aryl,
- 2) heterocycle,
- 3) OR⁶,
- 4) SR^{6a}, SO₂R^{6a}, or
- 5) ;

10

R⁶ and R⁷ are independently selected from:

- a) hydrogen,
- b) C_{1-C6} alkyl, C_{2-C6} alkenyl, C_{2-C6} alkynyl, C_{1-C6} perfluoroalkyl, F, Cl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- c) C_{1-C6} alkyl substituted by C_{1-C6} perfluoroalkyl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,

20

R⁸ is independently selected from:

- a) hydrogen,
- b) C_{1-C6} alkyl, C_{2-C6} alkenyl, C_{2-C6} alkynyl, C_{1-C6} perfluoroalkyl, F, Cl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- c) C_{1-C6} alkyl substituted by C_{1-C6} perfluoroalkyl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,

30

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R^{9a} is hydrogen or methyl;

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

5

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, O, -N(R¹⁰)-, or S(O)_m;

10

V is selected from:

- a) hydrogen,
- b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,
- c) aryl,
- d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- e) C₂-C₂₀ alkenyl, and

20

provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

X is -CH₂-;

25

Z is selected from:

- 1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:
 - a) C₁-4 alkyl, unsubstituted or substituted with: C₁-4 alkoxy, NR⁶R⁷, C₃-6 cycloalkyl, aryl, heterocycle, HO, -S(O)_mR^{6a}, or -C(O)NR⁶R⁷,
 - b) aryl or heterocycle,

30

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c) halogen,

d) OR⁶,

e) NR⁶R⁷,

f) CN,

5 g) NO₂,

h) CF₃;

i) -S(O)_mR^{6a},

j) -C(O)NR⁶R⁷, or

k) C₃-C₆ cycloalkyl; or

10 2) unsubstituted C₁-C₆ alkyl, substituted C₁-C₆ alkyl,
unsubstituted C₃-C₆ cycloalkyl or substituted C₃-C₆
cycloalkyl, wherein the substituted C₁-C₆ alkyl and substituted
C₃-C₆ cycloalkyl is substituted with one or two of the
following:

15 a) C₁-4 alkoxy,

b) NR⁶R⁷,

c) C₃-6 cycloalkyl,

d) -NR⁶C(O)R⁷,

e) HO,

20 f) -S(O)_mR^{6a},

g) halogen, or

h) perfluoroalkyl;

m is 0, 1 or 2;

25 n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4; and

r is 0 to 5, provided that r is 0 when V is hydrogen;

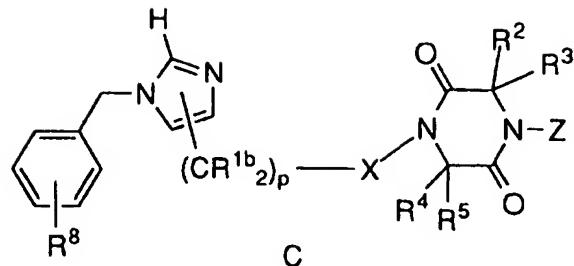
or a pharmaceutically acceptable salt thereof.

30

4. The compound according to Claim 3 of the formula

C:

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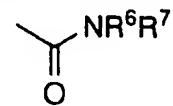
wherein:

R^{1b} is independently selected from:

- 5 a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, $R^{10}O-$, $-N(R^{10})_2$ or C_2-C_6 alkenyl,
- c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O-$, or $-N(R^{10})_2$;

10

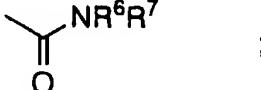
R^3 and R^5 are independently selected from H and CH_3 ;



R^2 and R^4 are independently selected from H; NR^6R^7 ; or C_1-C_5 alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

15

- 1) aryl,
- 2) heterocycle,
- 3) OR^6 ,
- 4) SR^{6a} , SO_2R^{6a} , or
- 5) NR^6R^7



20

R^6 and R^7 are independently selected from:

- a) hydrogen,
- b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O-$, $R^{10}C(O)NR^{10}-$, CN, NO₂,

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(R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or
R¹¹OC(O)NR¹⁰-, and

- 5 c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R¹⁰O-,
R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-,
R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R⁸ is independently selected from:

- a) hydrogen,
b) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆
10 perfluoroalkyl, F, Cl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, CN, NO₂,
(R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or
R¹¹OC(O)NR¹⁰-, and
c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R¹⁰O-,
R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-,
15 -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and
aryl;

20 R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

X is -CH₂-;

Z is selected from:

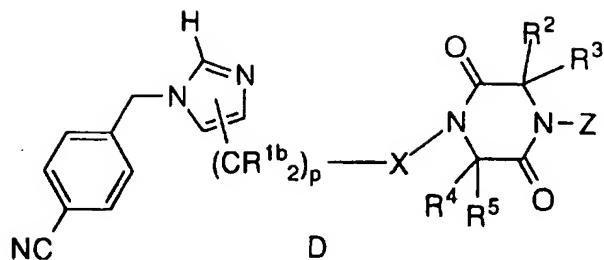
- 25 1) a unsubstituted or substituted group selected from aryl,
heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl,
heteroarylsulfonyl, wherein the substituted group is substituted
with one or more of the following:
a) C₁-4 alkyl, unsubstituted or substituted with:
30 C₁-4 alkoxy, NR⁶R⁷, C₃-6 cycloalkyl, aryl,
heterocycle, HO, -S(O)_mR^{6a}, or -C(O)NR⁶R⁷,
b) aryl or heterocycle,
c) halogen,
d) OR⁶,

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- e) NR^6R^7 ,
 - f) CN,
 - g) NO_2 ,
 - h) CF_3 ;
 - 5 i) $-\text{S}(\text{O})_m\text{R}^6\text{a}$,
 - j) $-\text{C}(\text{O})\text{NR}^6\text{R}^7$, or
 - k) $\text{C}_3\text{-C}_6$ cycloalkyl; or
- 2) unsubstituted $\text{C}_1\text{-C}_6$ alkyl, substituted $\text{C}_1\text{-C}_6$ alkyl,
unsubstituted $\text{C}_3\text{-C}_6$ cycloalkyl or substituted $\text{C}_3\text{-C}_6$
10 cycloalkyl, wherein the substituted $\text{C}_1\text{-C}_6$ alkyl and substituted
 $\text{C}_3\text{-C}_6$ cycloalkyl is substituted with one or two of the
following:
- a) $\text{C}_1\text{-4}$ alkoxy,
 - b) NR^6R^7 ,
 - c) $\text{C}_3\text{-6}$ cycloalkyl,
 - d) $-\text{NR}^6\text{C}(\text{O})\text{R}^7$,
 - e) HO,
 - f) $-\text{S}(\text{O})_m\text{R}^6\text{a}$,
 - 15 g) halogen, or
 - h) perfluoroalkyl;
- 20 m is 0, 1 or 2; and
p is 0, 1, 2, 3 or 4;
- 25 or an optical isomer or pharmaceutically acceptable salt thereof.

5. The compound according to Claim 3 of the formula
D:

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wherein:

R^{1b} is independently selected from:

- 5 a) hydrogen,
 b) aryl, heterocycle, cycloalkyl, $R^{10}O-$, $-N(R^{10})_2$ or C₂-C₆
 alkenyl,
 c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
 heterocycle, cycloalkyl, alkenyl, $R^{10}O-$, or $-N(R^{10})_2$;

10 R^2 and R^4 are independently selected from: hydrogen or C₁-C₆ alkyl;

R^3 and R^5 are hydrogen;

15 R^6 and R^7 are independently selected from:

- a) hydrogen,
 b) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆
 perfluoroalkyl, F, Cl, $R^{10}O-$, $R^{10}C(O)NR^{10}-$, CN, NO₂,
 (R^{10})₂N-C(NR¹⁰)-, $R^{10}C(O)-$, $R^{10}OC(O)-$, $-N(R^{10})_2$, or
 20 $R^{11}OC(O)NR^{10}-$, and
 c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, $R^{10}O-$,
 $R^{10}C(O)NR^{10}-$, (R^{10})₂N-C(NR¹⁰)-, $R^{10}C(O)-$,
 $R^{10}OC(O)-$, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$;

25 R^{10} is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and
 aryl;

R^{11} is independently selected from C₁-C₆ alkyl and aryl;

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X is -CH₂-;

- Z is mono- or bicyclic aryl, mono- or bicyclic heteroaryl,
mono- or bicyclic arylmethyl, mono- or bicyclic
5 heteroarylmethyl, mono- or bicyclic arylsulfonyl,
mono- or bicyclic heteroarylsulfonyl, unsubstituted or
substituted with one or two of the following:
1) C₁-4 alkyl, unsubstituted or substituted with:
10 a) C₁-4 alkoxy,
b) NR⁶R⁷,
c) C₃-6 cycloalkyl,
d) aryl or heterocycle,
e) HO,
f) -S(O)_mR⁶, or
15 g) -C(O)NR⁶R⁷,
2) aryl or heterocycle,
3) halogen,
4) OR⁶,
5) NR⁶R⁷,
20 6) CN,
7) NO₂,
8) CF₃;
9) -S(O)_mR⁶,
10) -C(O)NR⁶R⁷, or
25 11) C₃-C₆ cycloalkyl;

m is 0, 1 or 2; and

p is 0, 1, 2, 3 or 4;

30 or pharmaceutically acceptable salt thereof.

6. A compound which inhibits farnesyl-protein transferase which is:

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4-[1-(4-Cyanobenzyl)-5-imidazolylmethyl]-1-(3-chlorophenyl)-piperazine-2,5-dione

5 **(S)-3-n-Butyl-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-(3-chlorophenyl)piperazine-2,5-dione**

1-(3-Chlorophenyl)-4-[(3-(4-cyanobenzyl)pyridin-4-yl)methyl]piperazin-2,5-dione

10 **4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-phenylpiperazine-2,5-dione or**

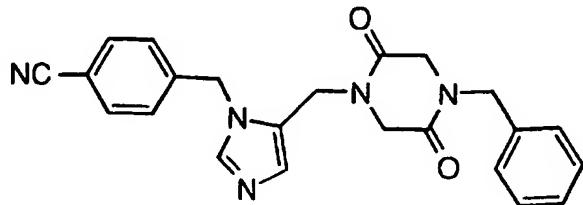
4-benzyl-1-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-piperazine-2,5-dione

15

or a pharmaceutically acceptable salt or optical isomer thereof.

7. The compound according to Claim 6 which is:

20 **4-benzyl-1-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-piperazine-2,5-dione**



25 **or a pharmaceutically acceptable salt thereof.**

8. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 1.

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9. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 2.

5

10. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 3.

10

11. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 6.

15

. 12. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 8.

20

13. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 9.

25

14. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

30

15. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 11.

16. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 8.

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17. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 9.

5 18. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

10 19. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 11.

15 20. A method for treating neurofibromin benign proliferative disorder which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 8.

20 21. A method for treating blindness related to retinal vascularization which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 8.

25 22. A method for treating infections from hepatitis delta and related viruses which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 8.

23. A method for preventing restenosis which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 8.

30 24. A method for treating polycystic kidney disease which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 8.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/04711

A. CLASSIFICATION OF SUBJECT MATTER IPC(6) :C07D 403/00; A61K 31/495 US CL :544/359; 514/255 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 544/359; 514/255		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Please See Extra Sheet.		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,287,195 A (HEERES ET AL.) 01 September 1981, see entire document.	1-11
A	US 4,456,605 A (HEERES ET AL.) 26 June 1984, see entire document.	1-11
A	US 5,478,934 A (YUAN ET AL.) 26 December 1995, see entire document.	1-11
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
<ul style="list-style-type: none"> * Special categories of cited documents: *'A' document defining the general state of the art which is not considered to be of particular relevance *'B' earlier document published on or after the international filing date *'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reasons (as specified) *'O' document referring to an oral disclosure, use, exhibition or other means *'P' document published prior to the international filing date but later than the priority date claimed 		<ul style="list-style-type: none"> *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art *A* document member of the same patent family
Date of the actual completion of the international search 11 JULY 1997	Date of mailing of the international search report 04 AUG 1997	
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer FLOYD D. HIGEL  Telephone No. (703) 308-1235	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/04711

B. FIELDS SEARCHED

Documentation other than minimum documentation that are included in the fields searched:

**CHEMICAL ABSTRACTS
INDEX CHemicus
CURRENT ABSTRACTS OF CHEMISTRY**

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